RNA INTERFERENCE MEDIATED TREATMENT OF POLYGLUTAMINE (POLYQ) REPEAT EXPANSION DISEASES USING SHORT INTERFERING NUCLEIC ACID (siNA)

This application is a continuation-in-part of U.S. Patent Application No. 10/757,803, filed January 14, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/720,448, filed November 24, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/693,059, filed October 23, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/444,853, filed May 23, 2003 and a continuation-in-part of 10/652,791, filed August 29, 2003, which is a continuation of 10/422,704, filed April 24, 2003, which is a continuation of U.S. Patent Application No. 10/417,012, filed April 16, 2003. This application is also a continuation-in-part of International Patent Application No. PCT/US03/05346, filed February 20, 2003, and a continuation-in-part of International Patent Application No. PCT/US03/05028, filed February 20, 2003, both of which claim the benefit of U.S. Provisional Application No. 60/358,580 filed February 20, 2002, U.S. Provisional Application No. 60/363,124 filed March 11, 2002, U.S. Provisional Application No. 60/386,782 filed June 6, 2002, U.S. Provisional Application No. 60/406,784 filed August 29, 2002, U.S. Provisional Application No. 60/408,378 filed September 5, 2002, U.S. Provisional Application No. 60/409,293 filed September 9, 2002, and U.S. Provisional Application No. 60/440,129 filed January 15, 2003. This application is also a continuation-in-part of US Patent Application No. 10/427,160, filed April 30, 2003 and International Patent Application No. PCT/US02/15876 filed May 17, 2002. The instant application claims the benefit of all the listed applications, which are hereby incorporated by reference herein in their entireties, including the drawings.

Field Of The Invention

The present invention concerns compounds, compositions, and methods for the study, diagnosis, and treatment of diseases and conditions associated with polyglutamine repeat (polyQ) allelic variants that respond to the modulation of gene expression and/or activity. The present invention also concerns compounds, compositions, and methods relating to diseases and conditions associated with polyglutamine repeat (polyQ) allelic

variants that respond to the modulation of expression and/or activity of genes involved in polyQ repeat gene expression pathways or other cellular processes that mediate the maintenance or development of polyQ repeat diseases and conditions. Specifically, the invention relates to small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules capable of mediating RNA interference (RNAi) against the expression disease related genes or alleles having polyQ repeat sequences.

Background Of The Invention

The following is a discussion of relevant art pertaining to RNAi. The discussion is provided only for understanding of the invention that follows. The summary is not an admission that any of the work described below is prior art to the claimed invention.

RNA interference refers to the process of sequence-specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, Cell, 101, 25-33; Fire *et al.*, 1998, *Nature,* 391, 806; Hamilton *et al.*, 1999, *Science*, 286, 950-951). The corresponding process in plants is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes and is commonly shared by diverse flora and phyla (Fire *et al.*, 1999, *Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or from the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response though a mechanism that has yet to be fully characterized. This mechanism appears to be different from the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2',5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L.

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as dicer. Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Hamilton *et al., supra*; Zamore *et al.,* 2000, Cell, 101, 25-33; Berstein *et al.,* 2001, *Nature,* 409, 363). Short interfering RNAs derived from dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes (Hamilton *et al., supra*; Elbashir *et al.,* 2001, *Genes Dev.,* 15, 188). Dicer has also been implicated in the excision of 21- and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.,* 2001, *Science,* 293, 834). The RNAi response also features an endonuclease complex, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence complementary to the antisense strand of the siRNA duplex. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex (Elbashir *et al.,* 2001, *Genes Dev.,* 15, 188).

RNAi has been studied in a variety of systems. Fire *et al.,* 1998, *Nature,* 391, 806, were the first to observe RNAi in *C. elegans*. Bahramian and Zarbl, 1999, *Molecular and Cellular Biology*, 19, 274-283 and Wianny and Goetz, 1999, *Nature Cell Biol.,* 2, 70, describe RNAi mediated by dsRNA in mammalian systems. Hammond *et al.,* 2000, *Nature,* 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA. Elbashir *et al.,* 2001, *Nature,* 411, 494 and Tuschl *et al.,* International PCT Publication No. WO 01/75164, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in Drosophila embryonic lysates (Elbashir *et al.,* 2001, *EMBO J.,* 20, 6877 and Tuschl *et al.,* International PCT Publication No. WO 01/75164) has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21-nucleotide siRNA duplexes are most active when containing 3'-terminal dinucleotide overhangs. Furthermore, complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of the 3'-terminal siRNA overhang nucleotides with 2'-deoxy nucleotides (2'-H) was shown to be tolerated. Single mismatch sequences in the center of the siRNA duplex were also

shown to abolish RNAi activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end of the guide sequence (Elbashir *et al.,* 2001, *EMBO J.,* 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA (Nykanen *et al.,* 2001, *Cell,* 107, 309).

Studies have shown that replacing the 3'-terminal nucleotide overhanging segments of a 21-mer siRNA duplex having two-nucleotide 3'-overhangs with deoxyribonucleotides does not have an adverse effect on RNAi activity. Replacing up to four nucleotides on each end of the siRNA with deoxyribonucleotides has been reported to be well tolerated, whereas complete substitution with deoxyribonucleotides results in no RNAi activity (Elbashir *et al.,* 2001, *EMBO J.,* 20, 6877 and Tuschl *et al.,* International PCT Publication No. WO 01/75164). In addition, Elbashir *et al., supra,* also report that substitution of siRNA with 2'-O-methyl nucleotides completely abolishes RNAi activity. Li *et al.,* International PCT Publication No. WO 00/44914, and Beach *et al.,* International PCT Publication No. WO 01/68836 preliminarily suggest that siRNA may include modifications to either the phosphate-sugar backbone or the nucleoside to include at least one of a nitrogen or sulfur heteroatom, however, neither application postulates to what extent such modifications would be tolerated in siRNA molecules, nor provides any further guidance or examples of such modified siRNA. Kreutzer *et al.,* Canadian Patent Application No. 2,359,180, also describe certain chemical modifications for use in dsRNA constructs in order to counteract activation of double-stranded RNA-dependent protein kinase PKR, specifically 2'-amino or 2'-O-methyl nucleotides, and nucleotides containing a 2'-O or 4'-C methylene bridge. However, Kreutzer *et al.* similarly fails to provide examples or guidance as to what extent these modifications would be tolerated in dsRNA molecules.

Parrish *et al.,* 2000, *Molecular Cell,* 6, 1077-1087, tested certain chemical modifications targeting the unc-22 gene in *C. elegans* using long (>25 nt) siRNA transcripts. The authors describe the introduction of thiophosphate residues into these siRNA transcripts by incorporating thiophosphate nucleotide analogs with T7 and T3 RNA polymerase and observed that RNAs with two phosphorothioate modified bases

also had substantial decreases in effectiveness as RNAi. Further, Parrish *et al.* reported that phosphorothioate modification of more than two residues greatly destabilized the RNAs *in vitro* such that interference activities could not be assayed. *Id.* at 1081. The authors also tested certain modifications at the 2'-position of the nucleotide sugar in the long siRNA transcripts and found that substituting deoxynucleotides for ribonucleotides produced a substantial decrease in interference activity, especially in the case of Uridine to Thymidine and/or Cytidine to deoxy-Cytidine substitutions. *Id.* In addition, the authors tested certain base modifications, including substituting, in sense and antisense strands of the siRNA, 4-thiouracil, 5-bromouracil, 5-iodouracil, and 3-(aminoallyl)uracil for uracil, and inosine for guanosine. Whereas 4-thiouracil and 5-bromouracil substitution appeared to be tolerated, Parrish reported that inosine produced a substantial decrease in interference activity when incorporated in either strand. Parrish also reported that incorporation of 5-iodouracil and 3-(aminoallyl)uracil in the antisense strand resulted in a substantial decrease in RNAi activity as well.

The use of longer dsRNA has been described. For example, Beach *et al.*, International PCT Publication No. WO 01/68836, describes specific methods for attenuating gene expression using endogenously-derived dsRNA. Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe a *Drosophila in vitro* RNAi system and the use of specific siRNA molecules for certain functional genomic and certain therapeutic applications; although Tuschl, 2001, *Chem. Biochem.*, 2, 239-245, doubts that RNAi can be used to cure genetic diseases or viral infection due to the danger of activating interferon response. Li *et al.*, International PCT Publication No. WO 00/44914, describe the use of specific long (141 bp-488 bp) enzymatically synthesized or vector expressed dsRNAs for attenuating the expression of certain target genes. Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646, describe certain methods for inhibiting the expression of particular genes in mammalian cells using certain long (550 bp-714 bp), enzymatically synthesized or vector expressed dsRNA molecules. Fire *et al.*, International PCT Publication No. WO 99/32619, describe particular methods for introducing certain long dsRNA molecules into cells for use in inhibiting gene expression in nematodes. Plaetinck *et al.*, International PCT Publication No. WO 00/01846, describe certain methods for identifying specific genes responsible for conferring a particular phenotype in a cell using specific long dsRNA molecules.

Mello *et al.*, International PCT Publication No. WO 01/29058, describe the identification of specific genes involved in dsRNA-mediated RNAi. Deschamps Depaillette *et al.*, International PCT Publication No. WO 99/07409, describe specific compositions consisting of particular dsRNA molecules combined with certain anti-viral agents. Waterhouse *et al.*, International PCT Publication No. 99/53050, describe certain methods for decreasing the phenotypic expression of a nucleic acid in plant cells using certain dsRNAs. Driscoll *et al.*, International PCT Publication No. WO 01/49844, describe specific DNA expression constructs for use in facilitating gene silencing in targeted organisms.

Others have reported on various RNAi and gene-silencing systems. For example, Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, describe specific chemically-modified dsRNA constructs targeting the unc-22 gene of *C. elegans*. Grossniklaus, International PCT Publication No. WO 01/38551, describes certain methods for regulating polycomb gene expression in plants using certain dsRNAs. Churikov *et al.*, International PCT Publication No. WO 01/42443, describe certain methods for modifying genetic characteristics of an organism using certain dsRNAs. Cogoni *et al.*, International PCT Publication No. WO 01/53475, describe certain methods for isolating a Neurospora silencing gene and uses thereof. Reed *et al.*, International PCT Publication No. WO 01/68836, describe certain methods for gene silencing in plants. Honer *et al.*, International PCT Publication No. WO 01/70944, describe certain methods of drug screening using transgenic nematodes as Parkinson's Disease models using certain dsRNAs. Deak *et al.*, International PCT Publication No. WO 01/72774, describe certain *Drosophila*-derived gene products that may be related to RNAi in *Drosophila*. Arndt *et al.*, International PCT Publication No. WO 01/92513 describe certain methods for mediating gene suppression by using factors that enhance RNAi. Tuschl *et al.*, International PCT Publication No. WO 02/44321, describe certain synthetic siRNA constructs. Pachuk *et al.*, International PCT Publication No. WO 00/63364, and Satishchandran *et al.*, International PCT Publication No. WO 01/04313, describe certain methods and compositions for inhibiting the function of certain polynucleotide sequences using certain long (over 250 bp), vector expressed dsRNAs. Echeverri *et al.*, International PCT Publication No. WO 02/38805, describe certain *C. elegans* genes identified via RNAi. Kreutzer *et al.*, International PCT Publications Nos. WO

02/055692, WO 02/055693, and EP 1144623 B1 describes certain methods for inhibiting gene expression using dsRNA. Graham *et al.*, International PCT Publications Nos. WO 99/49029 and WO 01/70949, and AU 4037501 describe certain vector expressed siRNA molecules. Fire *et al.*, US 6,506,559, describe certain methods for inhibiting gene expression in vitro using certain long dsRNA (299 bp-1033 bp) constructs that mediate RNAi. Martinez *et al.*, 2002, *Cell*, 110, 563-574, describe certain single stranded siRNA constructs, including certain 5'-phosphorylated single stranded siRNAs that mediate RNA interference in Hela cells. Harborth *et al.*, 2003, Antisense & Nucleic Acid Drug Development, 13, 83-105, describe certain chemically and structurally modified siRNA molecules. Chiu and Rana, 2003, RNA, 9, 1034-1048, describe certain chemically and structurally modified siRNA molecules. Miller *et al.*, 2003, *PNAS*, 100, 7195-7200, describe certain transcribed siRNA molecules targeting certain allele specific RNA transcripts associated with trinucleotide reapeat/polyQ nuerodegenerative disorders such as Machado Joseph Disease, spinocerebellar ataxia, and frontotemporaral dementia. Davidson *et al.*, WO 04/013280, describe certain siRNA molecules targeting certain allele specific RNA transcripts including certain polyQ repeat gene transcripts associated with certain neurodegenerative diseases.

SUMMARY OF THE INVENTION

This invention relates to compounds, compositions, and methods useful for modulating the expression of repeat expansion genes associated with the maintenance or development of neurodegenerative disease, for example polyglutamine repeat expansion genes and variants thereof, including single nucleotide polymorphism (SNP) variants associated with disease related trinucleotide repeat expansion genes, using short interfering nucleic acid (siNA) molecules. This invention also relates to compounds, compositions, and methods useful for modulating the expression and activity of repeat expansion genes, or other genes involved in pathways of repeat expansion genes expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of repeat expansion genes. A

siNA of the invention can be unmodified or chemically-modified. A siNA of the instant invention can be chemically synthesized, expressed from a vector or enzymatically synthesized. The instant invention also features various chemically-modified synthetic short interfering nucleic acid (siNA) molecules capable of modulating repeat expansion gene expression or activity in cells by RNA interference (RNAi). The use of chemically-modified siNA improves various properties of native siNA molecules through increased resistance to nuclease degradation *in vivo* and/or through improved cellular uptake. Further, contrary to earlier published studies, siNA having multiple chemical modifications retains its RNAi activity. The siNA molecules of the instant invention provide useful reagents and methods for a variety of therapeutic, diagnostic, target validation, genomic discovery, genetic engineering, and pharmacogenomic applications.

In one embodiment, the invention features one or more siNA molecules and methods that independently or in combination modulate the expression of repeat expansion genes encoding proteins, such as proteins comprising polyglutamine repeat expansions, associated with the maintenance and/or development of neurodegenerative diseases, such as genes encoding sequences comprising those sequences referred to by GenBank Accession Nos. shown in **Table I**, referred to herein generally as repeat expansion (RE) genes. The description below of the various aspects and embodiments of the invention is provided with reference to exemplary Huntingtin gene referred to herein as HD. However, the various aspects and embodiments are also directed to other repeat expansion genes, such spinocerebellar ataxia genes including SCA1, SCA2, SCA3, SCA5, SCA7, SCA12, and SCA17, spinal and bulbar muscular atrophy genes such as androgen receptor *(AR)* locus Xq11-q12 genes, and dentatorubropallidoluysian atrophy genes such as DRPLA, as well as other mutant gene variants having trinucleotide repeat expansions and SNPs associated with such trinucleotide repeat expansions.. The various aspects and embodiments are also directed to other genes that are involved in RE mediated pathways of signal transduction or gene expression that are involved in the progression, development, and/or maintenance of disease (e.g., Huntington disease, spinocerebellar ataxia, spinal and bulbar muscular dystrophy, and dentatorubropallidoluysian atrophy), including enzymes involved in processing RE proteins. These additional genes can be analyzed for target sites using the methods described for HD genes herein. Thus, the modulation of other genes and the effects of

such modulation of the other genes can be performed, determined, and measured as described herein.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a repeat expansion (RE) gene, wherein said siNA molecule comprises about 19 to about 21 base pairs.

In one embodiment, the invention features a siNA molecule that down-regulates expression of a RE gene, for example, wherein the RE gene comprises RE encoding sequence. In one embodiment, the invention features a siNA molecule that down-regulates expression of a RE gene, for example, wherein the RE gene comprises RE non-coding sequence or regulatory elements involved in RE gene expression.

In one embodiment, the invention features a siNA molecule having RNAi activity against RE RNA, wherein the siNA molecule comprises a sequence complementary to any RNA having RE encoding sequence, such as those sequences having GenBank Accession Nos. shown in **Table I**. In another embodiment, the invention features a siNA molecule having RNAi activity against RE RNA, wherein the siNA molecule comprises a sequence complementary to an RNA having other RE encoding sequence, for example other mutant RE genes not shown in Table I but known in the art to be associated with the development or maintenance of repeat expansion diseases and conditions, such as Huntington disease, spinocerebellar ataxia, spinal and bulbar muscular dystrophy, and dentatorubropallidoluysian atrophy. Chemical modifications as shown in **Tables III and IV** or otherwise described herein can be applied to any siNA construct of the invention. In another embodiment, a siNA molecule of the invention includes nucleotide sequence that can interact with nucleotide sequence of a RE gene and thereby mediate silencing of RE gene expression, for example, wherein the siNA mediates regulation of RE gene expression by cellular processes that modulate the chromatin structure of the RE gene and prevent transcription of the RE gene.

In one embodiment, siNA molecules of the invention are used to down regulate or inhibit the expression of mutant RE proteins that are neurotoxic, such as mutant RE proteins resulting from polyglutamine repeat expansions and fragments or portions of such mutant RE proteins that are processed by cellular enzymes resulting in neurotoxic

proteins or peptides. Analysis of RE genes, or RE protein or RNA levels can be used to identify subjects with Huntington disease or at risk of developing Huntington disease. These subjects are amenable to treatment, for example, treatment with siNA molecules of the invention and any other composition useful in treating Huntington disease. As such, analysis of RE protein or RNA levels can be used to determine treatment type and the course of therapy in treating a subject. Monitoring of RE protein or RNA levels can be used to predict treatment outcome and to determine the efficacy of compounds and compositions that modulate the level and/or activity of certain RE proteins associated with disease.

In another embodiment, the invention features a siNA molecule comprising nucleotide sequence, for example, nucleotide sequence in the antisense region of the siNA molecule that is complementary to a nucleotide sequence or portion of sequence of a RE gene. In another embodiment, the invention features a siNA molecule comprising a region, for example, the antisense region of the siNA construct, complementary to a sequence comprising a RE gene sequence or a portion thereof.

In one embodiment, the antisense region of RE siNA constructs can comprise a sequence complementary to sequence having any of SEQ ID NOs. 1-1752 and 3505-3511. In one embodiment, the antisense region can also comprise sequence having any of SEQ ID NOs. 1753-3504, 3513, 3515, 3517, 3530-3535, 3542-3547, 3554-3559, 3570, 3572, 3574, or 3577. In another embodiment, the sense region of the RE constructs can comprise sequence having any of SEQ ID NOs. 1-1752, 3505-3511, 3512, 3514, 3516, 3524-3529, 3536-3541, 3548-3553, 3569, 3571, 3573, 3575, or 3576. The sense region can comprise a sequence of SEQ ID NO. 3560 and the antisense region can comprise a sequence of SEQ ID NO. 3561. The sense region can comprise a sequence of SEQ ID NO. 3562 and the antisense region can comprise a sequence of SEQ ID NO. 3563. The sense region can comprise a sequence of SEQ ID NO. 3564 and the antisense region can comprise a sequence of SEQ ID NO. 3565. The sense region can comprise a sequence of SEQ ID NO. 3566 and the antisense region can comprise a sequence of SEQ ID NO. 3563. The sense region can comprise a sequence of SEQ ID NO. 3567 and the antisense region can comprise a sequence of SEQ ID NO. 3563. The sense region can

comprise a sequence of SEQ ID NO. 3566 and the antisense region can comprise a sequence of SEQ ID NO. 3568.

In one embodiment, a siNA molecule of the invention comprises any of SEQ ID NOs. 1-3577. The sequences shown in SEQ ID NOs: 1-3577 are not limiting. A siNA molecule of the invention can comprise any contiguous RE sequence (e.g., about 19 to about 25, or about 19, 20, 21, 22, 23, 24 or 25 contiguous RE nucleotides).

In yet another embodiment, the invention features a siNA molecule comprising a sequence, for example, the antisense sequence of the siNA construct, complementary to a sequence or portion of sequence comprising sequence represented by GenBank Accession Nos. shown in **Table I**. Chemical modifications in **Tables III and IV** and descrbed herein can be applied to any siNA costruct of the invention.

In one embodiment of the invention a siNA molecule comprises an antisense strand having about 19 to about 29 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29) nucleotides, wherein the antisense strand is complementary to a RNA sequence encoding a RE protein, and wherein said siNA further comprises a sense strand having about 19 to about 29 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29) nucleotides, and wherein said sense strand and said antisense strand are distinct nucleotide sequences with at least about 19 complementary nucleotides.

In another embodiment of the invention a siNA molecule of the invention comprises an antisense region having about 19 to about 29 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29) nucleotides, wherein the antisense region is complementary to a RNA sequence encoding a RE protein, and wherein said siNA further comprises a sense region having about 19 to about 29 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein said sense region and said antisense region comprise a linear molecule with at least about 19 complementary nucleotides.

In one embodiment of the invention a siNA molecule comprises an antisense strand comprising a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof encoding a RE protein. The siNA further comprises a sense strand,

wherein said sense strand comprises a nucleotide sequence of a RE gene or a portion thereof.

In another embodiment, a siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence encoding a RE protein or a portion thereof. The siNA molecule further comprises a sense region, wherein said sense region comprises a nucleotide sequence of a RE gene or a portion thereof.

In one embodiment, a siNA molecule of the invention has RNAi activity that modulates expression of RNA encoded by a RE gene. Because RE genes can share some degree of sequence homology with each other, siNA molecules can be designed to target a class of RE genes or alternately specific RE genes (e.g., SNP variants) by selecting sequences that are either shared amongst different RE targets or alternatively that are unique for a specific RE target. Therefore, in one embodiment, the siNA molecule can be designed to target conserved regions of RE RNA sequence having homology between several RE gene variants so as to target a class of RE genes (e.g., RE variants having differing trinucleotide repeat expansions) with one siNA molecule. Accordingly, in one embodiment, the siNA molecule of the invention modulates the expression of one or both RE alleles in a subject. In another embodiment, the siNA molecule can be designed to target a sequence that is unique to a specific RE RNA sequence (e.g., a single RE allele or RE SNP) due to the high degree of specificity that the siNA molecule requires to mediate RNAi activity

In one embodiment, nucleic acid molecules of the invention that act as mediators of the RNA interference gene silencing response are double-stranded nucleic acid molecules. In another embodiment, the siNA molecules of the invention consist of duplexes containing about 19 base pairs between oligonucleotides comprising about 19 to about 25 (*e.g.*, about 19, 20, 21, 22, 23, 24 or 25) nucleotides. In yet another embodiment, siNA molecules of the invention comprise duplexes with overhanging ends of about about 1 to about 3 (*e.g.*, about 1, 2, or 3) nucleotides, for example, about 21-nucleotide duplexes with about 19 base pairs and 3'-terminal mononucleotide, dinucleotide, or trinucleotide overhangs.

In one embodiment, the invention features one or more chemically-modified siNA constructs having specificity for RE expressing nucleic acid molecules, such as RNA encoding a RE protein. Non-limiting examples of such chemical modifications include without limitation phosphorothioate internucleotide linkages, 2'-deoxyribonucleotides, 2'-O-methyl ribonucleotides, 2'-deoxy-2'-fluoro ribonucleotides, "universal base" nucleotides, "acyclic" nucleotides, 5-C-methyl nucleotides, and terminal glyceryl and/or inverted deoxy abasic residue incorporation. These chemical modifications, when used in various siNA constructs, are shown to preserve RNAi activity in cells while at the same time, dramatically increasing the serum stability of these compounds. Furthermore, contrary to the data published by Parrish *et al., supra,* applicant demonstrates that multiple (greater than one) phosphorothioate substitutions are well-tolerated and confer substantial increases in serum stability for modified siNA constructs.

In one embodiment, a siNA molecule of the invention comprises modified nucleotides while maintaining the ability to mediate RNAi. The modified nucleotides can be used to improve *in vitro* or *in vivo* characteristics such as stability, activity, and/or bioavailability. For example, a siNA molecule of the invention can comprise modified nucleotides as a percentage of the total number of nucleotides present in the siNA molecule. As such, a siNA molecule of the invention can generally comprise about 5% to about 100% modified nucleotides (e.g., 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% modified nucleotides). The actual percentage of modified nucleotides present in a given siNA molecule will depend on the total number of nucleotides present in the siNA. If the siNA molecule is single stranded, the percent modification can be based upon the total number of nucleotides present in the single stranded siNA molecules. Likewise, if the siNA molecule is double stranded, the percent modification can be based upon the total number of nucleotides present in the sense strand, antisense strand, or both the sense and antisense strands.

One aspect of the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a RE gene. In one embodiment, a double stranded siNA molecule comprises one or more chemical modifications and

each strand of the double-stranded siNA is about 21 nucleotides long. In one embodiment, the double-stranded siNA molecule does not contain any ribonucleotides. In another embodiment, the double-stranded siNA molecule comprises one or more ribonucleotides. In one embodiment, each strand of the double-stranded siNA molecule comprises about 19 to about 23 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29) nucleotides, wherein each strand comprises about 19 nucleotides that are complementary to the nucleotides of the other strand. In one embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof of the RE gene, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence of the RE gene or a portion thereof.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a RE gene comprising an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of the RE gene or a portion thereof, and a sense region, wherein the sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of the RE gene or a portion thereof. In one embodiment, the antisense region and the sense region each comprise about 19 to about 23 (e.g. about 19, 20, 21, 22, or 23) nucleotides, wherein the antisense region comprises about 19 nucleotides that are complementary to nucleotides of the sense region.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a RE gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the RE gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region.

In one embodiment, a siNA molecule of the invention comprises blunt ends, i.e., ends that do not include any overhanging nucleotides. For example, a siNA molecule of the invention comprising modifications described herein (e.g., comprising nucleotides having Formulae I-VII or siNA constructs comprising Stab00-Stab22 or any combination

thereof) and/or any length described herein can comprise blunt ends or ends with no overhanging nucleotides.

In one embodiment, any siNA molecule of the invention can comprise one or more blunt ends, i.e. where a blunt end does not have any overhanging nucleotides. In a non-limiting example, a blunt ended siNA molecule has a number of base pairs equal to the number of nucleotides present in each strand of the siNA molecule. In another example, a siNA molecule comprises one blunt end, for example wherein the 5'-end of the antisense strand and the 3'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises one blunt end, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises two blunt ends, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand as well as the 5'-end of the antisense strand and 3'-end of the sense strand do not have any overhanging nucleotides. A blunt ended siNA molecule can comprise, for example, from about 18 to about 30 nucleotides (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides). Other nucleotides present in a blunt ended siNA molecule can comprise mismatches, bulges, loops, or wobble base pairs, for example, to modulate the activity of the siNA molecule to mediate RNA interference.

By "blunt ends" is meant symmetric termini or termini of a double stranded siNA molecule having no overhanging nucleotides. The two strands of a double stranded siNA molecule align with each other without over-hanging nucleotides at the termini. For example, a blunt ended siNA construct comprises terminal nucleotides that are complementary between the sense and antisense regions of the siNA molecule.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a RE gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. The sense region can be connected to the antisense region via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker.

In one embodiment, the invention features double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a repeat expansion (RE) gene, wherein the siNA molecule comprises about 19 to about 21 base pairs, and wherein each strand of the siNA molecule comprises one or more chemical modifications. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a RE gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of the RE gene. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a RE gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of the RE gene. In another embodiment, each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand. The RE gene can comprise, for example, huntingtin, SCA1, SCA2, SCA3, SCA6, SCA7, SCA12, SCA17, SBMA, or DRPLA (see for example Table I).

In one embodiment, a siNA molecule of the invention comprises no ribonucleotides. In another embodiment, a siNA molecule of the invention comprises ribonucleotides.

In one embodiment, a siNA molecule of the invention comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a RE gene or a portion thereof, and the siNA further comprises a sense region comprising a nucleotide sequence substantially similar to the nucleotide sequence of the RE gene or a portion thereof. In another embodiment, the antisense region and the sense region each comprise about 19 to about 23 nucleotides and the antisense region comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region. The RE gene can comprise, for example, huntingtin, SCA1, SCA2, SCA3, SCA6, SCA7, SCA12, SCA17, SBMA, or DRPLA (see for example Table I).

In one embodiment, a siNA molecule of the invention comprises a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence

that is complementary to a nucleotide sequence of RNA encoded by a RE gene, or a portion thereof, and the sense region comprises a nucleotide sequence that is complementary to the antisense region. In another embodiment, the siNA molecule is assembled from two separate oligonucleotide fragments, wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment, the sense region is connected to the antisense region via a linker molecule. In another embodiment, the sense region is connected to the antisense region via a linker molecule, such as a nucleotide or non-nucleotide linker. The RE gene can comprise, for example, huntingtin, SCA1, SCA2, SCA3, SCA6, SCA7, SCA12, SCA17, SBMA, or DRPLA (see for example Table I).

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a RE gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the RE gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region, and wherein the siNA molecule has one or more modified pyrimidine and/or purine nucleotides. In one embodiment, the pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine nucleotides or 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides. In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In one embodiment, the pyrimidine nucleotides in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the antisense region are 2'-O-methyl or 2'-deoxy purine nucleotides. In another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the sense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a RE gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule, and wherein the fragment comprising the sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment. In another embodiment, the terminal cap moiety is an inverted deoxy abasic moiety or glyceryl moiety. In another embodiment, each of the two fragments of the siNA molecule comprise about 21 nucleotides.

In one embodiment, the invention features a siNA molecule comprising at least one modified nucleotide, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. The siNA can be, for example, of length between about 12 and about 36 nucleotides. In another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro cytidine nucleotides. In another embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a method of increasing the stability of a siNA molecule against cleavage by ribonucleases comprising introducing at least one modified nucleotide into the siNA molecule, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. In another embodiment, all pyrimidine nucleotides present

in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro cytidine nucleotides. In another embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a RE gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the RE gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region, and wherein the purine nucleotides present in the antisense region comprise 2'-deoxy- purine nucleotides. In an alternative embodiment, the purine nucleotides present in the antisense region comprise 2'-O-methyl purine nucleotides. In either of the above embodiments, the antisense region can comprise a phosphorothioate internucleotide linkage at the 3' end of the antisense region. Alternatively, in either of the above embodiments, the antisense region can comprise a glyceryl modification at the 3' end of the antisense region. In another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the antisense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the antisense region of a siNA molecule of the invention comprises sequence complementary to a portion of a RE transcript having sequence

comprising the repeat expansion or a portion thereof and sequence unique to the particular RE disease related allele (e.g., huntingtin), such as sequence adjacent to the repeat expansion (e.g., adjacent to the 5' or 3' portion of the repeat expansion) or sequence comprising a SNP associated with the disease specific allele. As such, the antisense region of a siNA molecule of the invention can comprise sequence complementary to a repeat expansion region and adjacent sequences that are unique to a particular allele to provide specificity in mediating selective RNAi againt the disease related allele.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a RE gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule. In one embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine nucleotide, such as a 2'-deoxy-thymidine. In another embodiment, all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the RE gene. In another embodiment, about 21 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the RE gene. In any of the above embodiments, the 5'-end of the fragment comprising said antisense region can optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits the expression of a RE RNA sequence (e.g., wherein said target RNA sequence is encoded by a RE gene involved in the RE pathway), wherein the siNA molecule does not contain any ribonucleotides and wherein each strand of the double-stranded siNA molecule is about 21 nucleotides long.

Examples of non-ribonucleotide containing siNA constructs are combinations of stabilization chemistries shown in Table IV in any combination of Sense/Antisense chemistries, such as Stab 7/8, Stab 7/11, Stab 8/8, Stab 18/8, Stab 18/11, Stab 12/13, Stab 7/13, Stab 18/13, Stab 7/19, Stab 8/19, Stab 18/19, Stab 7/20, Stab 8/20, or Stab 18/20.

In one embodiment, the invention features a chemically synthesized double stranded RNA molecule that directs cleavage of a RE RNA via RNA interference, wherein each strand of said RNA molecule is about 21 to about 23 nucleotides in length; one strand of the RNA molecule comprises nucleotide sequence having sufficient complementarity to the RE RNA for the RNA molecule to direct cleavage of the RE RNA via RNA interference; and wherein at least one strand of the RNA molecule comprises one or more chemically modified nucleotides described herein, such as deoxynucleotides, 2'-O-methyl nucleotides, 2'-deoxy-2'-fluoro nucloetides, 2'-O-methoxyethyl nucleotides etc.

In one embodiment, the invention features a medicament comprising a siNA molecule of the invention.

In one embodiment, the invention features an active ingredient comprising a siNA molecule of the invention.

In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule to down-regulate expression of a RE gene, wherein the siNA molecule comprises one or more chemical modifications and each strand of the double-stranded siNA is about 18 to about 28 or more (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or more) nucleotides long.

In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a RE gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of RE RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and

wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a RE gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of RE RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a RE gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of RE RNA that encodes a protein or portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a RE gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of RE RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, each strand of the siNA molecule comprises about 18 to about 29 or more (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein each strand comprises at least about 18 nucleotides that are complementary to the nucleotides of the other strand. In another embodiment, the siNA molecule is assembled from two oligonucleotide fragments, wherein one fragment comprises the nucleotide sequence of the antisense strand of the siNA molecule and a

second fragment comprises nucleotide sequence of the sense region of the siNA molecule. In yet another embodiment, the sense strand is connected to the antisense strand via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker. In a further embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides. In still another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides. In another embodiment, the antisense strand comprises one or more 2'-deoxy-2'-fluoro pyrimidine nucleotides and one or more 2'-O-methyl purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-O-methyl purine nucleotides. In a further embodiment the sense strand comprises a 3'-end and a 5'-end, wherein a terminal cap moiety (e.g., an inverted deoxy abasic moiety or inverted deoxy nucleotide moiety such as inverted thymidine) is present at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand. In another embodiment, the antisense strand comprises a phosphorothioate internucleotide linkage at the 3' end of the antisense strand. In another embodiment, the antisense strand comprises a glyceryl modification at the 3' end. In another embodiment, the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a RE gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of RE RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein each of the two strands of the siNA molecule comprises about 21 nucleotides. In one embodiment, about 21

nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule, wherein at least two 3' terminal nucleotides of each strand of the siNA molecule are not base-paired to the nucleotides of the other strand of the siNA molecule. In another embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine, such as 2'-deoxy-thymidine. In another embodiment, each strand of the siNA molecule is base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the RE RNA or a portion thereof. In another embodiment, about 21 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the RE RNA or a portion thereof.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a RE gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of RE RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a RE gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of RE RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence or a portion thereof

of the antisense strand is complementary to a nucleotide sequence of the untranslated region or a portion thereof of the RE RNA.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a RE gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of RE RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand, wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence of the antisense strand is complementary to a nucleotide sequence of the RE RNA or a portion thereof that is present in the RE RNA.

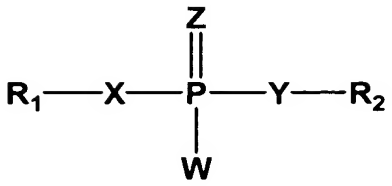
In one embodiment, the invention features a composition comprising a siNA molecule of the invention in a pharmaceutically acceptable carrier or diluent.

In a non-limiting example, the introduction of chemically-modified nucleotides into nucleic acid molecules provides a powerful tool in overcoming potential limitations of *in vivo* stability and bioavailability inherent to native RNA molecules that are delivered exogenously. For example, the use of chemically-modified nucleic acid molecules can enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect since chemically-modified nucleic acid molecules tend to have a longer half-life in serum. Furthermore, certain chemical modifications can improve the bioavailability of nucleic acid molecules by targeting particular cells or tissues and/or improving cellular uptake of the nucleic acid molecule. Therefore, even if the activity of a chemically-modified nucleic acid molecule is reduced as compared to a native nucleic acid molecule, for example, when compared to an all-RNA nucleic acid molecule, the overall activity of the modified nucleic acid molecule can be greater than that of the native molecule due to improved stability and/or delivery of the molecule. Unlike native unmodified siNA, chemically-modified siNA can also minimize the possibility of activating interferon activity in humans.

In any of the embodiments of siNA molecules described herein, the antisense region of a siNA molecule of the invention can comprise a phosphorothioate internucleotide linkage at the 3'-end of said antisense region. In any of the embodiments of siNA molecules described herein, the antisense region can comprise about one to about five phosphorothioate internucleotide linkages at the 5'-end of said antisense region. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs of a siNA molecule of the invention can comprise ribonucleotides or deoxyribonucleotides that are chemically-modified at a nucleic acid sugar, base, or backbone. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more universal base ribonucleotides. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more acyclic nucleotides.

One embodiment of the invention provides an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the invention in a manner that allows expression of the nucleic acid molecule. Another embodiment of the invention provides a mammalian cell comprising such an expression vector. The mammalian cell can be a human cell. The siNA molecule of the expression vector can comprise a sense region and an antisense region. The antisense region can comprise sequence complementary to a RNA or DNA sequence encoding RE and the sense region can comprise sequence complementary to the antisense region. The siNA molecule can comprise two distinct strands having complementary sense and antisense regions. The siNA molecule can comprise a single strand having complementary sense and antisense regions.

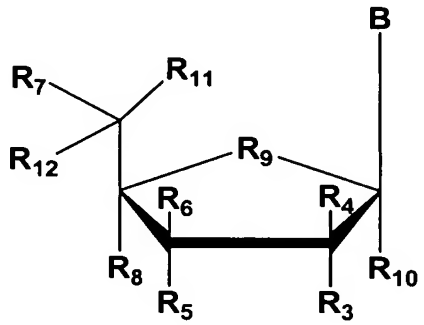
In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against a RE inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides comprising a backbone modified internucleotide linkage having Formula I:



wherein each R1 and R2 is independently any nucleotide, non-nucleotide, or polynucleotide which can be naturally-occurring or chemically-modified, each X and Y is independently O, S, N, alkyl, or substituted alkyl, each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, or acetyl and wherein W, X, Y, and Z are optionally not all O. In another embodiment, a backbone modification of the invention comprises a phosphonoacetate and/or thiophosphonoacetate internucleotide linkage (see for example Sheehan et al., 2003, Nucleic Acids Research, 31, 4109-4118).

The chemically-modified internucleotide linkages having Formula I, for example, wherein any Z, W, X, and/or Y independently comprises a sulphur atom, can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) chemically-modified internucleotide linkages having Formula I at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified internucleotide linkages having Formula I at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In another embodiment, a siNA molecule of the invention having internucleotide linkage(s) of Formula I also comprises a chemically-modified nucleotide or non-nucleotide having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against a RE inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula II:

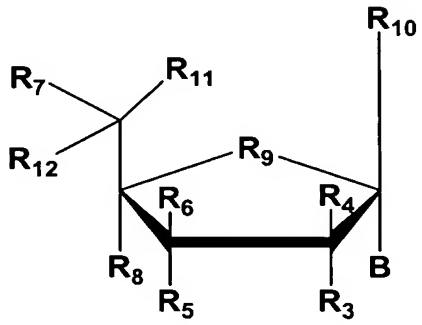


wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine, pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula II can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula II at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can

comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 5'-end of the sense strand, the antisense strand, or both strands. In anther non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 3'-end of the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against a RE inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula III:

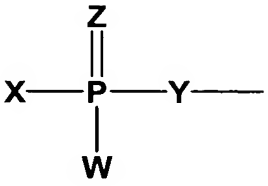


wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be employed to be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine, pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula III can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide(s) or non-nucleotide(s) of Formula III at the 5'-end of the sense strand, the antisense strand, or both strands. In anther non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end of the sense strand, the antisense strand, or both strands.

In another embodiment, a siNA molecule of the invention comprises a nucleotide having Formula II or III, wherein the nucleotide having Formula II or III is in an inverted configuration. For example, the nucleotide having Formula II or III is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against a RE inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a 5'-terminal phosphate group having Formula IV:



wherein each X and Y is independently O, S, N, alkyl, substituted alkyl, or alkylhalo; wherein each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, alkylhalo, or acetyl; and wherein W, X, Y and Z are not all O.

In one embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand, for example, a

strand complementary to a target RNA, wherein the siNA molecule comprises an all RNA siNA molecule. In another embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand wherein the siNA molecule also comprises about 1 to about 3 (*e.g.*, about 1, 2, or 3) nucleotide 3'-terminal nucleotide overhangs having about 1 to about 4 (*e.g.*, about 1, 2, 3, or 4) deoxyribonucleotides on the 3'-end of one or both strands. In another embodiment, a 5'-terminal phosphate group having Formula IV is present on the target-complementary strand of a siNA molecule of the invention, for example a siNA molecule having chemical modifications having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against a RE inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more phosphorothioate internucleotide linkages. For example, in a non-limiting example, the invention features a chemically-modified short interfering nucleic acid (siNA) having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in one siNA strand. In yet another embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) individually having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in both siNA strands. The phosphorothioate internucleotide linkages can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more phosphorothioate internucleotide linkages at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) consecutive phosphorothioate internucleotide linkages at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the sense strand comprises about 1 to about 5, specifically about 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro

nucleotides, with or without about 1 to about 5 or more, for example about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a siNA molecule, wherein the antisense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl,

2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5, for example about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule having about 1 to about 5, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages in each strand of the siNA molecule.

In another embodiment, the invention features a siNA molecule comprising 2'-5' internucleotide linkages. The 2'-5' internucleotide linkage(s) can be at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of one or both siNA sequence strands. In addition, the 2'-5' internucleotide linkage(s) can be present at various other positions within one or both siNA sequence strands, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a pyrimidine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a purine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage.

In another embodiment, a chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified, wherein each strand is about 18 to about 27 (*e.g.*, about 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) nucleotides in length, wherein the duplex has about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the chemical modification comprises a structure having any of Formulae I-VII. For example, an exemplary chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein each strand consists of about 21 nucleotides, each having a 2-nucleotide 3'-terminal nucleotide overhang, and

wherein the duplex has about 19 base pairs. In another embodiment, a siNA molecule of the invention comprises a single stranded hairpin structure, wherein the siNA is about 36 to about 70 (*e.g.*, about 36, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 19 base pairs and a 2-nucleotide 3'-terminal nucleotide overhang. In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. For example, a linear hairpin siNA molecule of the invention is designed such that degradation of the loop portion of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

In another embodiment, a siNA molecule of the invention comprises a hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 25 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 3 to about 23 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, a linear hairpin siNA molecule of the invention contains a stem

loop motif, wherein the loop portion of the siNA molecule is biodegradable. In another embodiment, a linear hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 20 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms an asymmetric hairpin structure having about 3 to about 18 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, an asymmetric hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. In another embodiment, an asymmetric hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

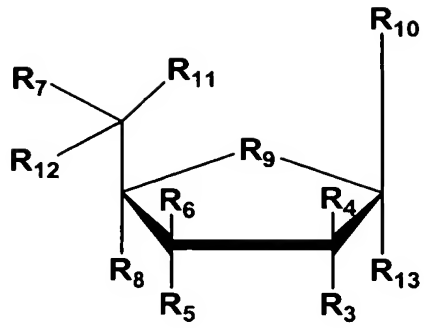
In another embodiment, a siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 16 to about 25 (*e.g.*, about 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) nucleotides in length, wherein the sense region is about 3 to about 18 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides in length, wherein the sense region and the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises an asymmetric double stranded structure having separate

polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 18 to about 22 (*e.g.*, about 18, 19, 20, 21, or 22) nucleotides in length and wherein the sense region is about 3 to about 15 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) nucleotides in length, wherein the sense region the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. In another embodiment, the asymmetic double stranded siNA molecule can also have a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV).

In another embodiment, a siNA molecule of the invention comprises a circular nucleic acid molecule, wherein the siNA is about 38 to about 70 (*e.g.*, about 38, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification, which comprises a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a circular oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein the circular oligonucleotide forms a dumbbell shaped structure having about 19 base pairs and 2 loops.

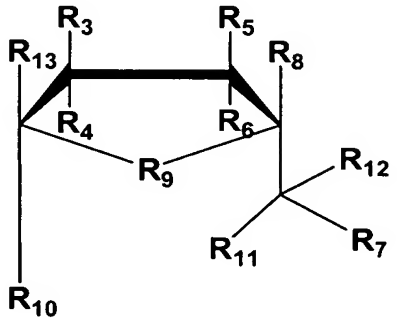
In another embodiment, a circular siNA molecule of the invention contains two loop motifs, wherein one or both loop portions of the siNA molecule is biodegradable. For example, a circular siNA molecule of the invention is designed such that degradation of the loop portions of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) abasic moiety, for example a compound having Formula V:



wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2.

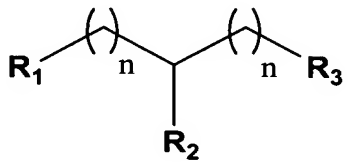
In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) inverted abasic moiety, for example a compound having Formula VI:



wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2,

and either R2, R3, R8 or R13 serve as points of attachment to the siNA molecule of the invention.

In another embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) substituted polyalkyl moieties, for example a compound having Formula VII:



wherein each n is independently an integer from 1 to 12, each R1, R2 and R3 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or a group having Formula I, and R1, R2 or R3 serves as points of attachment to the siNA molecule of the invention.

In another embodiment, the invention features a compound having Formula VII, wherein R1 and R2 are hydroxyl (OH) groups, n = 1, and R3 comprises O and is the point of attachment to the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both strands of a double-stranded siNA molecule of the invention or to a single-stranded siNA molecule of the invention. This modification is referred to herein as "glyceryl" (for example modification 6 in **Figure 10**).

In another embodiment, a moiety having any of Formula V, VI or VII of the invention is at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of a siNA molecule of the invention. For example, a moiety having Formula V, VI or VII can be present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense strand, the sense strand, or both antisense and sense strands of the siNA molecule. In addition, a moiety having Formula VII can be present at the 3'-end or the 5'-end of a hairpin siNA molecule as described herein.

In another embodiment, a siNA molecule of the invention comprises an abasic residue having Formula V or VI, wherein the abasic residue having Formula VI or VI is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) locked nucleic acid (LNA) nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In another embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) acyclic nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), wherein any nucleotides

comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said antisense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention capable of mediating RNA interference

(RNAi) against a RE inside a cell or reconstituted *in vitro* system comprising a sense region, wherein one or more pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), and an antisense region, wherein one or more pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). The sense region and/or the antisense region can have a terminal cap modification, such as any modification described herein or shown in **Figure 10**, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense and/or antisense sequence. The sense and/or antisense region can optionally further comprise a 3'-terminal nucleotide overhang having about 1 to about 4 (e.g., about 1, 2, 3, or 4) 2'-deoxynucleotides. The overhang nucleotides can further comprise one or more (e.g., about 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages. Non-limiting examples of these chemically-modified siNAs are shown in **Figures 4 and 5** and **Tables III and IV** herein. In any of these described embodiments, the purine nucleotides present in the sense region are alternatively 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides) and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Also, in any of these embodiments, one or more purine nucleotides present in the sense region are alternatively purine ribonucleotides (e.g., wherein all purine nucleotides are purine ribonucleotides or

alternately a plurality of purine nucleotides are purine ribonucleotides) and any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Additionally, in any of these embodiments, one or more purine nucleotides present in the sense region and/or present in the antisense region are alternatively selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides (e.g., wherein all purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides or alternately a plurality of purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides).

In another embodiment, any modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, comprise modified nucleotides having properties or characteristics similar to naturally occurring ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, are resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi. Non-limiting examples of nucleotides having a northern configuration include locked nucleic acid (LNA) nucleotides (e.g., 2′-O, 4′-C-methylene-(D-ribofuranosyl) nucleotides); 2'-methoxyethoxy (MOE) nucleotides; 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro nucleotides, 2'-deoxy-2'-chloro nucleotides, 2'-azido nucleotides, and 2'-O-methyl nucleotides.

In one embodiment, the sense strand of a double stranded siNA molecule of the invention comprises a terminal cap moiety, (see for example **Figure 10**) such as an

inverted deoxyabaisc moiety, at the 3'-end, 5'-end, or both 3' and 5'-ends of the sense strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid molecule (siNA) capable of mediating RNA interference (RNAi) against a RE inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a conjugate covalently attached to the chemically-modified siNA molecule. Non-limiting examples of conjugates contemplated by the invention include conjugates and ligands described in Vargeese *et al.*, USSN 10/427,160, filed April 30, 2003, incorporated by reference herein in its entirety, including the drawings. In another embodiment, the conjugate is covalently attached to the chemically-modified siNA molecule via a biodegradable linker. In one embodiment, the conjugate molecule is attached at the 3'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In another embodiment, the conjugate molecule is attached at the 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In yet another embodiment, the conjugate molecule is attached both the 3'-end and 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule, or any combination thereof. In one embodiment, a conjugate molecule of the invention comprises a molecule that facilitates delivery of a chemically-modified siNA molecule into a biological system, such as a cell. In another embodiment, the conjugate molecule attached to the chemically-modified siNA molecule is a polyethylene glycol, human serum albumin, or a ligand for a cellular receptor that can mediate cellular uptake. Examples of specific conjugate molecules contemplated by the instant invention that can be attached to chemically-modified siNA molecules are described in Vargeese *et al.*, U.S. Serial No. 10/201,394, incorporated by reference herein. The type of conjugates used and the extent of conjugation of siNA molecules of the invention can be evaluated for improved pharmacokinetic profiles, bioavailability, and/or stability of siNA constructs while at the same time maintaining the ability of the siNA to mediate RNAi activity. As such, one skilled in the art can screen siNA constructs that are modified with various conjugates to determine whether the siNA conjugate complex possesses improved properties while maintaining the ability to mediate RNAi, for example in animal models as are generally known in the art.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule of the invention, wherein the siNA further comprises a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the siNA to the antisense region of the siNA. In one embodiment, a nucleotide linker of the invention can be a linker of ≥ 2 nucleotides in length, for example about 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length. In another embodiment, the nucleotide linker can be a nucleic acid aptamer. By "aptamer" or "nucleic acid aptamer" as used herein is meant a nucleic acid molecule that binds specifically to a target molecule wherein the nucleic acid molecule has sequence that comprises a sequence recognized by the target molecule in its natural setting. Alternately, an aptamer can be a nucleic acid molecule that binds to a target molecule where the target molecule does not naturally bind to a nucleic acid. The target molecule can be any molecule of interest. For example, the aptamer can be used to bind to a ligand-binding domain of a protein, thereby preventing interaction of the naturally occurring ligand with the protein. This is a non-limiting example and those in the art will recognize that other embodiments can be readily generated using techniques generally known in the art. (See, for example, Gold *et al.,* 1995, *Annu. Rev. Biochem.,* 64, 763; Brody and Gold, 2000, *J. Biotechnol.,* 74, 5; Sun, 2000, *Curr. Opin. Mol. Ther.,* 2, 100; Kusser, 2000, *J. Biotechnol.,* 74, 27; Hermann and Patel, 2000, *Science,* 287, 820; and Jayasena, 1999, *Clinical Chemistry,* 45, 1628.)

In yet another embodiment, a non-nucleotide linker of the invention comprises abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, polyhydrocarbon, or other polymeric compounds (e.g. polyethylene glycols such as those having between 2 and 100 ethylene glycol units). Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res.* 1990, *18*:6353 and *Nucleic Acids Res.* 1987, *15*:3113; Cload and Schepartz, *J. Am. Chem. Soc.* 1991, *113*:6324; Richardson and Schepartz, *J. Am. Chem. Soc.* 1991, *113*:5109; Ma *et al., Nucleic Acids Res.* 1993, *21*:2585 and *Biochemistry* 1993, *32*:1751; Durand *et al., Nucleic Acids Res.* 1990, *18*:6353; McCurdy *et al., Nucleosides & Nucleotides* 1991, *10*:287; Jschke *et al., Tetrahedron Lett.* 1993, *34*:301; Ono *et al., Biochemistry* 1991, *30*:9914; Arnold *et al.,* International Publication No. WO 89/02439; Usman *et al.,* International Publication No. WO 95/06731; Dudycz *et al.,* International Publication No. WO 95/11910 and Ferentz and Verdine, *J. Am. Chem. Soc.* 1991, *113*:4000, all hereby incorporated by reference

herein. A "non-nucleotide" further means any group or compound that can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound can be abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine, for example at the C1 position of the sugar.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) inside a cell or reconstituted in vitro system, wherein one or both strands of the siNA molecule that are assembled from two separate oligonucleotides do not comprise any ribonucleotides. For example, a siNA molecule can be assembled from a single oligonculeotide where the sense and antisense regions of the siNA comprise separate oligonucleotides not having any ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotides. In another example, a siNA molecule can be assembled from a single oligonculeotide where the sense and antisense regions of the siNA are linked or circularized by a nucleotide or non-nucleotide linker as desrcibed herein, wherein the oligonucleotide does not have any ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotide. Applicant has surprisingly found that the presense of ribonucleotides (e.g., nucleotides having a 2'-hydroxyl group) within the siNA molecule is not required or essential to support RNAi activity. As such, in one embodiment, all positions within the siNA can include chemically modified nucleotides and/or non-nucleotides such as nucleotides and or non-nucleotides having Formula I, II, III, IV, V, VI, or VII or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA molecule that mediates RNAi activity in a cell or reconstituted in vitro system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group and a 3'-terminal phosphate group (e.g., a 2',3'-cyclic phosphate). In another embodiment, the

single stranded siNA molecule of the invention comprises about 19 to about 29 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29) nucleotides. In yet another embodiment, the single stranded siNA molecule of the invention comprises one or more chemically modified nucleotides or non-nucleotides described herein. For example, all the positions within the siNA molecule can include chemically-modified nucleotides such as nucleotides having any of Formulae I-VII, or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA molecule that mediates RNAi activity in a cell or reconstituted in vitro systemcomprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence, wherein one or more pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and a terminal cap modification, such as any modification described herein or shown in **Figure 10**, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense sequence. The siNA optionally further comprises about 1 to about 4 or more (e.g., about 1, 2, 3, 4 or more) terminal 2'-deoxynucleotides at the 3'-end of the siNA molecule, wherein the terminal nucleotides can further comprise one or more (e.g., 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages, and wherein the siNA optionally further comprises a terminal phosphate group, such as a 5'-terminal phosphate group. In any of these embodiments, any purine nucleotides present in the antisense region are alternatively 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA (i.e., purine nucleotides present in the sense and/or antisense region) can alternatively be locked nucleic acid (LNA) nucleotides (e.g., wherein all purine nucleotides are LNA nucleotides or alternately a plurality of purine

portion thereof. The siNA can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (i.e. each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double stranded structure, for example wherein the double stranded region is about 19 base pairs); the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. Alternatively, the siNA is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s). The siNA can be a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The siNA can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof, and wherein the circular polynucleotide can be processed either *in vivo* or *in vitro* to generate an active siNA molecule capable of mediating RNAi. The siNA can also comprise a single stranded polynucleotide having nucleotide sequence complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof (for example, where such siNA molecule does not require the presence within the siNA molecule of nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof), wherein the single stranded polynucleotide can further comprise a terminal phosphate group, such as a 5'-phosphate (see for example Martinez *et al.*, 2002, *Cell.*, 110, 563-574 and Schwarz *et al.*, 2002, *Molecular Cell*, 10, 537-568), or 5',3'-diphosphate. In certain embodiment, the siNA molecule of the invention comprises

separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, van der waals interactions, hydrophobic intercations, and/or stacking interactions. In certain embodiments, the siNA molecules of the invention comprise nucleotide sequence that is complementary to nucleotide sequence of a target gene. In another embodiment, the siNA molecule of the invention interacts with nucleotide sequence of a target gene in a manner that causes inhibition of expression of the target gene. As used herein, siNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically-modified nucleotides and non-nucleotides. In certain embodiments, the short interfering nucleic acid molecules of the invention lack 2'-hydroxy (2'-OH) containing nucleotides. Applicant describes in certain embodiments short interfering nucleic acids that do not require the presence of nucleotides having a 2'-hydroxy group for mediating RNAi and as such, short interfering nucleic acid molecules of the invention optionally do not include any ribonucleotides (e.g., nucleotides having a 2'-OH group). Such siNA molecules that do not require the presence of ribonucleotides within the siNA molecule to support RNAi can however have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. Optionally, siNA molecules can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. The modified short interfering nucleic acid molecules of the invention can also be referred to as short interfering modified oligonucleotides "siMON." As used herein, the term siNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically-modified siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics. For example, siNA molecules of the invention can be used to epigenetically silence genes at both the post-transcriptional level or the

pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siNA molecules of the invention can result from siNA mediated modification of chromatin structure to alter gene expression (see, for example, Verdel *et al.,* 2004, *Science,* 303, 672-676; Pal-Bhadra *et al.,* 2004, *Science,* 303, 669-672; Allshire, 2002, *Science,* 297, 1818-1819; Volpe *et al.,* 2002, *Science,* 297, 1833-1837; Jenuwein, 2002, *Science,* 297, 2215-2218; and Hall *et al.,* 2002, *Science,* 297, 2232-2237).

In one embodiment, a siNA molecule of the invention is a duplex forming oligonucleotide "DFO", (see for example **Figures 14-15** and Vaish *et al.,* USSN 10/727,780 filed December 3, 2003).

In one embodiment, a siNA molecule of the invention is a multifunctional siNA, (see for example **Figures 16-22** and Jadhati *et al.,* USSN (TBD) filed February 10, 2004). The multifunctional siNA of the invention can comprise sequence targeting, for example, two regions of HD RNA (see for example target sequences in **Tables II and III**), such as HD sequence comprising a trinucleotide repeat region of the RNA and a SNP region of the RNA.

By "asymmetric hairpin" as used herein is meant a linear siNA molecule comprising an antisense region, a loop portion that can comprise nucleotides or non-nucleotides, and a sense region that comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex with loop. For example, an asymmetric hairpin siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g., about 19, 20, 21, or 22) nucleotides) and a loop region comprising about 4 to about 8 (e.g., about 4, 5, 6, 7, or 8) nucleotides, and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region. The asymmetric hairpin siNA molecule can also comprise a 5'-terminal phosphate group that can be chemically modified. The loop portion of the asymmetric hairpin siNA molecule can comprise nucleotides, non-nucleotides, linker molecules, or conjugate molecules as described herein.

By "asymmetric duplex" as used herein is meant a siNA molecule having two separate strands comprising a sense region and an antisense region, wherein the sense region comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex. For example, an asymmetric duplex siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g. about 19, 20, 21, or 22) nucleotides) and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region.

By "modulate" is meant that the expression of the gene, or level of RNA molecule or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits is up regulated or down regulated, such that expression, level, or activity is greater than or less than that observed in the absence of the modulator. For example, the term "modulate" can mean "inhibit," but the use of the word "modulate" is not limited to this definition.

By "inhibit", "down-regulate", or "reduce", it is meant that the expression of the gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, is reduced below that observed in the absence of the nucleic acid molecules (e.g., siNA) of the invention. In one embodiment, inhibition, down-regulation or reduction with an siNA molecule is below that level observed in the presence of an inactive or attenuated molecule. In another embodiment, inhibition, down-regulation, or reduction with siNA molecules is below that level observed in the presence of, for example, an siNA molecule with scrambled sequence or with mismatches. In another embodiment, inhibition, down-regulation, or reduction of gene expression with a nucleic acid molecule of the instant invention is greater in the presence of the nucleic acid molecule than in its absence.

By "gene", or "target gene", is meant, a nucleic acid that encodes an RNA, for example, nucleic acid sequences including, but not limited to, structural genes encoding a polypeptide. A gene or target gene can also encode a functional RNA (fRNA) or non-coding RNA (ncRNA), such as small temporal RNA (stRNA), micro RNA (miRNA),

small nuclear RNA (snRNA), short interfering RNA (siRNA), small nucleolar RNA (snRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and precursor RNAs thereof. Such non-coding RNAs can serve as target nucleic acid molecules for siNA mediated RNA interference in modulating the activity of fRNA or ncRNA involved in functional or regulatory cellular processes. Abberant fRNA or ncRNA activity leading to disease can therefore be modulated by siNA molecules of the invention. siNA molecules targeting fRNA and ncRNA can also be used to manipulate or alter the genotype or phenotype of an organism or cell, by intervening in cellular processes such as genetic imprinting, transcription, translation, or nucleic acid processing (e.g., transamination, methylation etc.). The target gene can be a gene derived from a cell, an endogenous gene, a transgene, or exogenous genes such as genes of a pathogen, for example a virus, which is present in the cell after infection thereof. The cell containing the target gene can be derived from or contained in any organism, for example a plant, animal, protozoan, virus, bacterium, or fungus. Non-limiting examples of plants include monocots, dicots, or gymnosperms. Non-limiting examples of animals include vertebrates or invertebrates. Non-limiting examples of fungi include molds or yeasts.

By "repeat expansion" or "RE" as used herein is meant, any protein, peptide, or polypeptide comprising a trinucleotide repeat expansion that is associated with the maintenance or development of a polyQ disease, such as Huntington disease, spinocerebellar ataxia, spinal and bulbar muscular dystrophy, and dentatorubropallidoluysian atrophy, for example as encoded by Genbank Accession Nos. shown in **Table I**. The terms "repeat expansion" or "RE" also refer to nucleic acid sequences encloding any protein, peptide, or polypeptide comprising a trinucleotide repeat expansion, such as RNA or DNA comprising trinucleotide repeat expansion encoding sequence (see for example Wood *et al.,* 2003, Neuropathol Appl Neurobiol., 29, 529-45).

By "Huntingtin" or "HD" as used herein is meant, any Huntingtin protein, peptide, or polypeptide associated with the deveopment or maintenence of Huntington disease. The terms "Huntingtin" and "HD" also refer to nucleic acid sequences encloding any huntingtin protein, peptide, or polypeptide, such as Huntingtin RNA or Huntingtin DNA (see for example Van Dellen *et al.,* January 24, 2004, Neurogenetics).

By "homologous sequence" is meant, a nucleotide sequence that is shared by one or more polynucleotide sequences, such as genes, gene transcripts and/or non-coding polynucleotides. For example, a homologous sequence can be a nucleotide sequence that is shared by two or more genes encoding related but different proteins, such as different members of a gene family, different protein epitopes, different protein isoforms or completely divergent genes, such as a cytokine and its corresponding receptors. A homologous sequence can be a nucleotide sequence that is shared by two or more non-coding polynucleotides, such as noncoding DNA or RNA, regulatory sequences, introns, and sites of transcriptional control or regulation. Homologous sequences can also include conserved sequence regions shared by more than one polynucleotide sequence. Homology does not need to be perfect homology (e.g., 100%), as partially homologous sequences are also contemplated by the instant invention (e.g., 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80% etc.).

By "conserved sequence region" is meant, a nucleotide sequence of one or more regions in a polynucleotide does not vary significantly between generations or from one biological system or organism to another biological system or organism. The polynucleotide can include both coding and non-coding DNA and RNA.

By "sense region" is meant a nucleotide sequence of a siNA molecule having complementarity to an antisense region of the siNA molecule. In addition, the sense region of a siNA molecule can comprise a nucleic acid sequence having homology with a target nucleic acid sequence.

By "antisense region" is meant a nucleotide sequence of a siNA molecule having complementarity to a target nucleic acid sequence. In addition, the antisense region of a siNA molecule can optionally comprise a nucleic acid sequence having complementarity to a sense region of the siNA molecule.

By "target nucleic acid" is meant any nucleic acid sequence whose expression or activity is to be modulated. The target nucleic acid can be DNA or RNA.

By "complementarity" is meant that a nucleic acid can form hydrogen bond(s) with another nucleic acid sequence by either traditional Watson-Crick or other non-traditional types. In reference to the nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., RNAi activity. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner *et al.*, 1987, *CSH Symp. Quant. Biol.* LII pp.123-133; Frier *et al.*, 1986, *Proc. Nat. Acad. Sci.* USA 83:9373-9377; Turner *et al.*, 1987, *J. Am. Chem. Soc.* 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule that can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, or 10 nucleotides out of a total of 10 nucleotides in the first oligonuelcotide being based paired to a second nucleic acid sequence having 10 nucleotides represents 50%, 60%, 70%, 80%, 90%, and 100% complementary respectively). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

The siNA molecules of the invention represent a novel therapeutic approach to treat Huntington disease and related conditions such as progressive chorea, rigidity, and dementia, and seizures, and any other diseases or conditions that are related to or will respond to the levels of huntingtin in a cell or tissue, alone or in combination with other therapies. The reduction of huntingtin expression (specifically alleles associated with Huntington disease, such as polyglutamine repeat expansion and related SNPs) and thus reduction in the level of the respective protein relieves, to some extent, the symptoms of the disease or condition.

In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently about 18 to about 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (*e.g.*, about 17, 18, 19, 20, 21, 22 or 23). In yet another embodiment, siNA molecules of the invention comprising hairpin or circular structures are about 35 to about 55 (*e.g.*, about 35, 40, 45, 50 or 55) nucleotides in length, or about 38 to about 44

(*e.g.*, 38, 39, 40, 41, 42, 43 or 44) nucleotides in length and comprising about 16 to about 22 (*e.g.*, about 16, 17, 18, 19, 20, 21 or 22) base pairs. Exemplary siNA molecules of the invention are shown in **Table II**. Exemplary synthetic siNA molecules of the invention are shown in **Table III** and/or **Figures 4-5**.

As used herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism, e.g., specifically does not refer to a human. The cell can be present in an organism, e.g., birds, plants and mammals such as humans, cows, sheep, apes, monkeys, swine, dogs, and cats. The cell can be prokaryotic (e.g., bacterial cell) or eukaryotic (e.g., mammalian or plant cell). The cell can be of somatic or germ line origin, totipotent or pluripotent, dividing or non-dividing. The cell can also be derived from or can comprise a gamete or embryo, a stem cell, or a fully differentiated cell.

The siNA molecules of the invention are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, infusion pump or stent, with or without their incorporation in biopolymers. In particular embodiments, the nucleic acid molecules of the invention comprise sequences shown in **Tables II-III** and/or **Figures 4-5**. Examples of such nucleic acid molecules consist essentially of sequences defined in these tables and figures. Furthermore, the chemically modified constructs described in **Table IV** can be applied to any siNA sequence of the invention.

In another aspect, the invention provides mammalian cells containing one or more siNA molecules of this invention. The one or more siNA molecules can independently be targeted to the same or different sites.

By "RNA" is meant a molecule comprising at least one ribonucleotide residue. By "ribonucleotide" is meant a nucleotide with a hydroxyl group at the 2' position of a β-D-ribo-furanose moiety. The terms include double-stranded RNA, single-stranded RNA, isolated RNA such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA, as well as altered RNA that differs from naturally occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides. Such alterations can include addition of non-nucleotide material, such as to

the end(s) of the siNA or internally, for example at one or more nucleotides of the RNA. Nucleotides in the RNA molecules of the instant invention can also comprise non-standard nucleotides, such as non-naturally occurring nucleotides or chemically synthesized nucleotides or deoxynucleotides. These altered RNAs can be referred to as analogs or analogs of naturally-occurring RNA.

By "subject" is meant an organism, which is a donor or recipient of explanted cells or the cells themselves. "Subject" also refers to an organism to which the nucleic acid molecules of the invention can be administered. A subject can be a mammal or mammalian cells, including a human or human cells.

The term "phosphorothioate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise a sulfur atom. Hence, the term phosphorothioate refers to both phosphorothioate and phosphorodithioate internucleotide linkages.

The term "phosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise an acetyl or protected acetyl group.

The term "thiophosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z comprises an acetyl or protected acetyl group and W comprises a sulfur atom or alternately W comprises an acetyl or protected acetyl group and Z comprises a sulfur atom.

The term "universal base" as used herein refers to nucleotide base analogs that form base pairs with each of the natural DNA/RNA bases with little discrimination between them. Non-limiting examples of universal bases include C-phenyl, C-naphthyl and other aromatic derivatives, inosine, azole carboxamides, and nitroazole derivatives such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole as known in the art (see for example Loakes, 2001, *Nucleic Acids Research,* 29, 2437-2447).

The term "acyclic nucleotide" as used herein refers to any nucleotide having an acyclic ribose sugar, for example where any of the ribose carbons (C1, C2, C3, C4, or C5), are independently or in combination absent from the nucleotide.

The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed herein (e.g., cancers and othe proliferative conditions). For example, to treat a particular disease or condition, the siNA molecules can be administered to a subject or can be administered to other appropriate cells evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment.

In a further embodiment, the siNA molecules can be used in combination with other known treatments to treat conditions or diseases discussed above. For example, the described molecules could be used in combination with one or more known therapeutic agents to treat a disease or condition. Non-limiting examples of other therapeutic agents that can be readily combined with a siNA molecule of the invention are enzymatic nucleic acid molecules, allosteric nucleic acid molecules, antisense, decoy, or aptamer nucleic acid molecules, antibodies such as monoclonal antibodies, small molecules, and other organic and/or inorganic compounds including metals, salts and ions.

In one embodiment, the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the invention, in a manner which allows expression of the siNA molecule. For example, the vector can contain sequence(s) encoding both strands of a siNA molecule comprising a duplex. The vector can also contain sequence(s) encoding a single nucleic acid molecule that is self-complementary and thus forms a siNA molecule. Non-limiting examples of such expression vectors are described in Paul *et al.*, 2002, *Nature Biotechnology,* 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology,* 19, 497; Lee *et al.*, 2002, *Nature Biotechnology,* 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online publication doi:10.1038/nm725.

In another embodiment, the invention features a mammalian cell, for example, a human cell, including an expression vector of the invention.

In yet another embodiment, the expression vector of the invention comprises a sequence for a siNA molecule having complementarity to a RNA molecule referred to by a Genbank Accession numbers, for example Genbank Accession Nos. shown in **Table I**.

In one embodiment, an expression vector of the invention comprises a nucleic acid sequence encoding two or more siNA molecules, which can be the same or different.

In another aspect of the invention, siNA molecules that interact with target RNA molecules and down-regulate gene encoding target RNA molecules (for example target RNA molecules referred to by Genbank Accession numbers herein) are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecules bind and down-regulate gene function or expression via RNA interference (RNAi). Delivery of siNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that would allow for introduction into the desired target cell.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a non-limiting example of a scheme for the synthesis of siNA molecules. The complementary siNA sequence strands, strand 1 and strand 2, are synthesized in tandem and are connected by a cleavable linkage, such as a nucleotide succinate or abasic succinate, which can be the same or different from the cleavable linker used for solid phase synthesis on a solid support. The synthesis can be either solid phase or solution phase, in the example shown, the synthesis is a solid phase synthesis. The synthesis is performed such that a protecting group, such as a dimethoxytrityl group,

remains intact on the terminal nucleotide of the tandem oligonucleotide. Upon cleavage and deprotection of the oligonucleotide, the two siNA strands spontaneously hybridize to form a siNA duplex, which allows the purification of the duplex by utilizing the properties of the terminal protecting group, for example by applying a trityl on purification method wherein only duplexes/oligonucleotides with the terminal protecting group are isolated.

Figure 2 shows a MALDI-TOF mass spectrum of a purified siNA duplex synthesized by a method of the invention. The two peaks shown correspond to the predicted mass of the separate siNA sequence strands. This result demonstrates that the siNA duplex generated from tandem synthesis can be purified as a single entity using a simple trityl-on purification methodology.

Figure 3 shows a non-limiting proposed mechanistic representation of target RNA degradation involved in RNAi. Double-stranded RNA (dsRNA), which is generated by RNA-dependent RNA polymerase (RdRP) from foreign single-stranded RNA, for example viral, transposon, or other exogenous RNA, activates the DICER enzyme that in turn generates siNA duplexes. Alternately, synthetic or expressed siNA can be introduced directly into a cell by appropriate means. An active siNA complex forms which recognizes a target RNA, resulting in degradation of the target RNA by the RISC endonuclease complex or in the synthesis of additional RNA by RNA-dependent RNA polymerase (RdRP), which can activate DICER and result in additional siNA molecules, thereby amplifying the RNAi response.

Figure 4A-F shows non-limiting examples of chemically-modified siNA constructs of the present invention. In the figure, N stands for any nucleotide (adenosine, guanosine, cytosine, uridine, or optionally thymidine, for example thymidine can be substituted in the overhanging regions designated by parenthesis (N N). Various modifications are shown for the sense and antisense strands of the siNA constructs.

Figure 4A: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein.

The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4B: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the sense and antisense strand.

Figure 4C: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-O-methyl or 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that

may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4D: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4E: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise

ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4F: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and having one 3'-terminal phosphorothioate internucleotide linkage and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-deoxy nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand. The antisense strand of constructs A-F comprise sequence complementary to any target nucleic acid sequence of the invention. Furthermore, when a glyceryl moiety (L) is present at the 3'-end of the antisense strand for any construct shown in Figure 4 A-F, the modified internucleotide linkage is optional.

Figure 5A-F shows non-limiting examples of specific chemically-modified siNA sequences of the invention. **A-F** applies the chemical modifications described in **Figure 4A-F** to a HD siNA sequence. Such chemical modifications can be applied to any repeat expansion sequence and/or related SNP sequence.

Figure 6 shows non-limiting examples of different siNA constructs of the invention. The examples shown (constructs 1, 2, and 3) have 19 representative base pairs; however, different embodiments of the invention include any number of base pairs

described herein. Bracketed regions represent nucleotide overhangs, for example comprising about 1, 2, 3, or 4 nucleotides in length, preferably about 2 nucleotides. Constructs 1 and 2 can be used independently for RNAi activity. Construct 2 can comprise a polynucleotide or non-nucleotide linker, which can optionally be designed as a biodegradable linker. In one embodiment, the loop structure shown in construct 2 can comprise a biodegradable linker that results in the formation of construct 1 *in vivo* and/or *in vitro*. In another example, construct 3 can be used to generate construct 2 under the same principle wherein a linker is used to generate the active siNA construct 2 *in vivo* and/or *in vitro*, which can optionally utilize another biodegradable linker to generate the active siNA construct 1 *in vivo* and/or *in vitro*. As such, the stability and/or activity of the siNA constructs can be modulated based on the design of the siNA construct for use *in vivo* or *in vitro* and/or *in vitro*.

Figure 7A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate siNA hairpin constructs.

Figure 7A: A DNA oligomer is synthesized with a 5'-restriction site (R1) sequence followed by a region having sequence identical (sense region of siNA) to a predetermined HD target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, which is followed by a loop sequence of defined sequence (X), comprising, for example, about 3 to about 10 nucleotides.

Figure 7B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence that will result in a siNA transcript having specificity for a HD target sequence and having self-complementary sense and antisense regions.

Figure 7C: The construct is heated (for example to about 95°C) to linearize the sequence, thus allowing extension of a complementary second DNA strand using a primer to the 3'-restriction sequence of the first strand. The double-stranded DNA is then inserted into an appropriate vector for expression in cells. The construct can be designed such that a 3'-terminal nucleotide overhang results from the transcription, for example by engineering restriction sites and/or utilizing a poly-U termination region as described in Paul *et al.*, 2002, *Nature Biotechnology,* 29, 505-508.

Figure 8A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate double-stranded siNA constructs.

Figure 8A: A DNA oligomer is synthesized with a 5'-restriction (R1) site sequence followed by a region having sequence identical (sense region of siNA) to a predetermined HD target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, and which is followed by a 3'-restriction site (R2) which is adjacent to a loop sequence of defined sequence (X).

Figure 8B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence.

Figure 8C: The construct is processed by restriction enzymes specific to R1 and R2 to generate a double-stranded DNA which is then inserted into an appropriate vector for expression in cells. The transcription cassette is designed such that a U6 promoter region flanks each side of the dsDNA which generates the separate sense and antisense strands of the siNA. Poly T termination sequences can be added to the constructs to generate U overhangs in the resulting transcript.

Figure 9A-E is a diagrammatic representation of a method used to determine target sites for siNA mediated RNAi within a particular target nucleic acid sequence, such as messenger RNA.

Figure 9A: A pool of siNA oligonucleotides are synthesized wherein the antisense region of the siNA constructs has complementarity to target sites across the target nucleic acid sequence, and wherein the sense region comprises sequence complementary to the antisense region of the siNA.

Figure 9B&C: (**Figure 9B**) The sequences are pooled and are inserted into vectors such that (**Figure 9C**) transfection of a vector into cells results in the expression of the siNA.

Figure 9D: Cells are sorted based on phenotypic change that is associated with modulation of the target nucleic acid sequence.

Figure 9E: The siNA is isolated from the sorted cells and is sequenced to identify efficacious target sites within the target nucleic acid sequence.

Figure 10 shows non-limiting examples of different stabilization chemistries (1-10) that can be used, for example, to stabilize the 3'-end of siNA sequences of the invention, including **(1)** [3-3']-inverted deoxyribose; **(2)** deoxyribonucleotide; **(3)** [5'-3']-3'-deoxyribonucleotide; **(4)** [5'-3']-ribonucleotide; **(5)** [5'-3']-3'-O-methyl ribonucleotide; **(6)** 3'-glyceryl; **(7)** [3'-5']-3'-deoxyribonucleotide; **(8)** [3'-3']-deoxyribonucleotide; **(9)** [5'-2']-deoxyribonucleotide; and **(10)** [5-3']-dideoxyribonucleotide. In addition to modified and unmodified backbone chemistries indicated in the figure, these chemistries can be combined with different backbone modifications as described herein, for example, backbone modifications having Formula I. In addition, the 2'-deoxy nucleotide shown 5' to the terminal modifications shown can be another modified or unmodified nucleotide or non-nucleotide described herein, for example modifications having any of Formulae I-VII or any combination thereof.

Figure 11 shows a non-limiting example of a strategy used to identify chemically modified siNA constructs of the invention that are nuclease resistance while preserving the ability to mediate RNAi activity. Chemical modifications are introduced into the siNA construct based on educated design parameters (e.g. introducing 2'-mofications, base modifications, backbone modifications, terminal cap modifications etc). The modified construct in tested in an appropriate system (e.g. human serum for nuclease resistance, shown, or an animal model for PK/delivery parameters). In parallel, the siNA construct is tested for RNAi activity, for example in a cell culture system such as a luciferase reporter assay). Lead siNA constructs are then identified which possess a particular characteristic while maintaining RNAi activity, and can be further modified and assayed once again. This same approach can be used to identify siNA-conjugate molecules with improved pharmacokinetic profiles, delivery, and RNAi activity.

Figure 12 shows non-limiting examples of phosphorylated siNA molecules of the invention, including linear and duplex constructs and asymmetric derivatives thereof.

Figure 13 shows non-limiting examples of chemically modified terminal phosphate groups of the invention.

Figure 14A shows a non-limiting example of methodology used to design self complementary DFO constructs utilizing palidrome and/or repeat nucleic acid sequences that are identifed in a target nucleic acid sequence. (i) A palindrome or repeat sequence is identified in a nucleic acid target sequence. (ii) A sequence is designed that is complementary to the target nucleic acid sequence and the palindrome sequence. (iii) An inverse repeat sequence of the non-palindrome/repeat portion of the complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complmentary DFO molecule comprising sequence complementary to the nucleic acid target. (iv) The DFO molecule can self-assemble to form a double stranded oligonucleotide. **Figure 14B** shows a non-limiting representative example of a duplex forming oligonucleotide sequence. **Figure 14C** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence. **Figure 14D** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence followed by interaction with a target nucleic acid sequence resulting in modulation of gene expression.

Figure 15 shows a non-limiting example of the design of self complementary DFO constructs utilizing palidrome and/or repeat nucleic acid sequences that are incorporated into the DFO constructs that have sequence complementary to any target nucleic acid sequence of interest. Incorporation of these palindrome/repeat sequences allow the design of DFO constructs that form duplexes in which each strand is capable of mediating modulation of target gene expression, for example by RNAi. First, the target sequence is identified. A complementary sequence is then generated in which nucleotide or non-nucleotide modifications (shown as X or Y) are introduced into the complementary sequence that generate an artificial palindrome (shown as XYXYXY in the Figure). An inverse repeat of the non-palindrome/repeat complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complmentary DFO comprising sequence complementary to the nucleic acid target. The DFO can self-assemble to form a double stranded oligonucleotide.

Figure 16 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure**

16A shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 16B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a frist target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 17 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure 17A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a frist target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 17B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a frist target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the

multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 16**.

Figure 18 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifuctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 18A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a frist target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 18B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a frist target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 19 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifuctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 19A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a frist target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 19B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a frist target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 18**.

Figure 20 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid molecules, such as separate RNA molecules encoding differing proteins, for example a cytokine and its corresponding receptor, differing viral strains, a virus and a cellular protein involved in viral infection or replication, or differing proteins involved in a common or divergent

biologic pathway that is implicated in the maintenance of progression of disease. Each strand of the multifunctional siNA construct comprises a region having complementarity to separate target nucleic acid molecules. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interferance mediated cleavage of its corresponding target. These design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

Figure 21 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid seqeunces within the same target nucleic acid molecule, such as alternate coding regions of a RNA, coding and non-coding regions of a RNA, or alternate splice variant regions of a RNA. Each strand of the multifunctional siNA construct comprises a region having complementarity to the separate regions of the target nucleic acid molecule. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interferance mediated cleavage of its corresponding target region. These design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

DETAILED DESCRIPTION OF THE INVENTION

Mechanism of action of Nucleic Acid Molecules of the Invention

The discussion that follows discusses the proposed mechanism of RNA interference mediated by short interfering RNA as is presently known, and is not meant to be limiting and is not an admission of prior art. Applicant demonstrates herein that

chemically-modified short interfering nucleic acids possess similar or improved capacity to mediate RNAi as do siRNA molecules and are expected to possess improved stability and activity *in vivo*; therefore, this discussion is not meant to be limiting only to siRNA and can be applied to siNA as a whole. By "improved capacity to mediate RNAi" or "improved RNAi activity" is meant to include RNAi activity measured *in vitro* and/or *in vivo* where the RNAi activity is a reflection of both the ability of the siNA to mediate RNAi and the stability of the siNAs of the invention. In this invention, the product of these activities can be increased *in vitro* and/or *in vivo* compared to an all RNA siRNA or a siNA containing a plurality of ribonucleotides. In some cases, the activity or stability of the siNA molecule can be decreased (i.e., less than ten-fold), but the overall activity of the siNA molecule is enhanced *in vitro* and/or *in vivo*.

RNA interference refers to the process of sequence specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Fire *et al.*, 1998, *Nature,* 391, 806). The corresponding process in plants is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes which is commonly shared by diverse flora and phyla (Fire *et al.*, 1999, *Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response though a mechanism that has yet to be fully characterized. This mechanism appears to be different from the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2', 5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L.

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as Dicer. Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Berstein *et al.*, 2001, *Nature,* 409, 363). Short interfering RNAs derived from Dicer activity are typically

about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes. Dicer has also been implicated in the excision of 21- and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.,* 2001, *Science,* 293, 834). The RNAi response also features an endonuclease complex containing a siRNA, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence homologous to the siRNA. Cleavage of the target RNA takes place in the middle of the region complementary to the guide sequence of the siRNA duplex (Elbashir *et al.,* 2001, *Genes Dev.,* 15, 188). In addition, RNA interference can also involve small RNA (e.g., micro-RNA or miRNA) mediated gene silencing, presumably though cellular mechanisms that regulate chromatin structure and thereby prevent transcription of target gene sequences (see for example Allshire, 2002, *Science,* 297, 1818-1819; Volpe *et al.,* 2002, *Science,* 297, 1833-1837; Jenuwein, 2002, *Science,* 297, 2215-2218; and Hall *et al.,* 2002, *Science,* 297, 2232-2237). As such, siNA molecules of the invention can be used to mediate gene silencing via interaction with RNA transcripts or alternately by interaction with particular gene sequences, wherein such interaction results in gene silencing either at the transcriptional level or post-transcriptional level.

RNAi has been studied in a variety of systems. Fire *et al.,* 1998, *Nature,* 391, 806, were the first to observe RNAi in *C. elegans*. Wianny and Goetz, 1999, *Nature Cell Biol.,* 2, 70, describe RNAi mediated by dsRNA in mouse embryos. Hammond *et al.,* 2000, *Nature,* 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA. Elbashir *et al.,* 2001, *Nature,* 411, 494, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in Drosophila embryonic lysates has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21 nucleotide siRNA duplexes are most active when containing two 2-nucleotide 3'-terminal nucleotide overhangs. Furthermore, substitution of one or both siRNA strands with 2'-deoxy or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of 3'-terminal siRNA nucleotides with deoxy nucleotides was shown to be tolerated. Mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi

activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA (Nykanen *et al.*, 2001, *Cell,* 107, 309); however, siRNA molecules lacking a 5'-phosphate are active when introduced exogenously, suggesting that 5'-phosphorylation of siRNA constructs may occur *in vivo*.

Synthesis of Nucleic acid Molecules

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small" refers to nucleic acid motifs no more than 100 nucleotides in length, preferably no more than 80 nucleotides in length, and most preferably no more than 50 nucleotides in length; *e.g.*, individual siNA oligonucleotide sequences or siNA sequences synthesized in tandem) are preferably used for exogenous delivery. The simple structure of these molecules increases the ability of the nucleic acid to invade targeted regions of protein and/or RNA structure. Exemplary molecules of the instant invention are chemically synthesized, and others can similarly be synthesized.

Oligonucleotides (*e.g.*, certain modified oligonucleotides or portions of oligonucleotides lacking ribonucleotides) are synthesized using protocols known in the art, for example as described in Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19, Thompson *et al.*, International PCT Publication No. WO 99/54459, Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684, Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, Brennan *et al.*, 1998, *Biotechnol Bioeng.*, 61, 33-45, and Brennan, U.S. Pat. No. 6,001,311. All of these references are incorporated herein by reference. The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 2.5 min coupling step for 2'-O-methylated nucleotides and a 45 second coupling step for 2'-deoxy nucleotides or 2'-deoxy-2'-fluoro nucleotides. **Table V** outlines the amounts and the contact times of the

reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M = 6.6 μmol) of 2'-O-methyl phosphoramidite and a 105-fold excess of S-ethyl tetrazole (60 μL of 0.25 M = 15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 22-fold excess (40 μL of 0.11 M = 4.4 μmol) of deoxy phosphoramidite and a 70-fold excess of S-ethyl tetrazole (40 μL of 0.25 M = 10 μmol) can be used in each coupling cycle of deoxy residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); and oxidation solution is 16.9 mM I_2, 49 mM pyridine, 9% water in THF (PERSEPTIVE™). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide, 0.05 M in acetonitrile) is used.

Deprotection of the DNA-based oligonucleotides is performed as follows: the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aqueous methylamine (1 mL) at 65 °C for 10 minutes. After cooling to –20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H2O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder.

The method of synthesis used for RNA including certain siNA molecules of the invention follows the procedure as described in Usman *et al.*, 1987, *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.*, 1990, *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684 Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, and

makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 7.5 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides. **Table V** outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M = 6.6 μmol) of 2'-O-methyl phosphoramidite and a 75-fold excess of S-ethyl tetrazole (60 μL of 0.25 M = 15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 66-fold excess (120 μL of 0.11 M = 13.2 μmol) of alkylsilyl (ribo) protected phosphoramidite and a 150-fold excess of S-ethyl tetrazole (120 μL of 0.25 M = 30 μmol) can be used in each coupling cycle of ribo residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution is 16.9 mM I_2, 49 mM pyridine, 9% water in THF (PERSEPTIVE™). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide0.05 M in acetonitrile) is used.

Deprotection of the RNA is performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to –20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H2O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to

a white powder. The base deprotected oligoribonucleotide is resuspended in anhydrous TEA/HF/NMP solution (300 µL of a solution of 1.5 mL N-methylpyrrolidinone, 750 µL TEA and 1 mL TEA•3HF to provide a 1.4 M HF concentration) and heated to 65 °C. After 1.5 h, the oligomer is quenched with 1.5 M NH_4HCO_3.

Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO: 1/1 (0.8 mL) at 65 °C for 15 minutes. The vial is brought to room temperature TEA•3HF (0.1 mL) is added and the vial is heated at 65 °C for 15 minutes. The sample is cooled at –20 °C and then quenched with 1.5 M NH_4HCO_3.

For purification of the trityl-on oligomers, the quenched NH_4HCO_3 solution is loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing the loaded cartridge with water, the RNA is detritylated with 0.5% TFA for 13 minutes. The cartridge is then washed again with water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide is then eluted with 30% acetonitrile.

The average stepwise coupling yields are typically >98% (Wincott *et al.,* 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96-well format.

Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example, by ligation (Moore *et al.,* 1992, *Science* 256, 9923; Draper *et al.,* International PCT publication No. WO 93/23569; Shabarova *et al.,* 1991, *Nucleic Acids Research* 19, 4247; Bellon *et al.,* 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon *et al.,* 1997, *Bioconjugate Chem.* 8, 204), or by hybridization following synthesis and/or deprotection.

The siNA molecules of the invention can also be synthesized via a tandem synthesis methodology as described in Example 1 herein, wherein both siNA strands are synthesized as a single contiguous oligonucleotide fragment or strand separated by a

cleavable linker which is subsequently cleaved to provide separate siNA fragments or strands that hybridize and permit purification of the siNA duplex. The linker can be a polynucleotide linker or a non-nucleotide linker. The tandem synthesis of siNA as described herein can be readily adapted to both multiwell/multiplate synthesis platforms such as 96 well or similarly larger multi-well platforms. The tandem synthesis of siNA as described herein can also be readily adapted to large scale synthesis platforms employing batch reactors, synthesis columns and the like.

A siNA molecule can also be assembled from two distinct nucleic acid strands or fragments wherein one fragment includes the sense region and the second fragment includes the antisense region of the RNA molecule.

The nucleic acid molecules of the present invention can be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-*C*-allyl, 2'-fluoro, 2'-*O*-methyl, 2'-H (for a review see Usman and Cedergren, 1992, *TIBS* 17, 34; Usman *et al.,* 1994, *Nucleic Acids Symp. Ser.* 31, 163). siNA constructs can be purified by gel electrophoresis using general methods or can be purified by high pressure liquid chromatography (HPLC; see Wincott *et al., supra*, the totality of which is hereby incorporated herein by reference) and re-suspended in water.

In another aspect of the invention, siNA molecules of the invention are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules.

Optimizing Activity of the nucleic acid molecule of the invention.

Chemically synthesizing nucleic acid molecules with modifications (base, sugar and/or phosphate) can prevent their degradation by serum ribonucleases, which can increase their potency (see *e.g.,* Eckstein *et al.,* International Publication No. WO 92/07065; Perrault *et al.,* 1990 *Nature* 344, 565; Pieken *et al.,* 1991, *Science* 253, 314; Usman and Cedergren, 1992, *Trends in Biochem. Sci.* 17, 334; Usman *et al.,*

International Publication No. WO 93/15187; and Rossi *et al.,* International Publication No. WO 91/03162; Sproat, U.S. Pat. No. 5,334,711; Gold *et al.,* U.S. Pat. No. 6,300,074; and Burgin *et al., supra;* all of which are incorporated by reference herein). All of the above references describe various chemical modifications that can be made to the base, phosphate and/or sugar moieties of the nucleic acid molecules described herein. Modifications that enhance their efficacy in cells, and removal of bases from nucleic acid molecules to shorten oligonucleotide synthesis times and reduce chemical requirements are desired.

There are several examples in the art describing sugar, base and phosphate modifications that can be introduced into nucleic acid molecules with significant enhancement in their nuclease stability and efficacy. For example, oligonucleotides are modified to enhance stability and/or enhance biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-*C*-allyl, 2'-fluoro, 2'-*O*-methyl, 2'-O-allyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992, *TIBS.* 17, 34; Usman *et al.,* 1994, *Nucleic Acids Symp. Ser.* 31, 163; Burgin *et al.,* 1996, *Biochemistry*, 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein *et al., International Publication* PCT No. WO 92/07065; Perrault *et al. Nature*, 1990, *344*, 565-568; Pieken *et al. Science,* 1991, *253*, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, *17*, 334-339; Usman *et al. International Publication* PCT No. WO 93/15187; Sproat, *U.S. Pat.* No. 5,334,711 and Beigelman *et al.,* 1995, *J. Biol. Chem.,* 270, 25702; Beigelman *et al.,* International PCT publication No. WO 97/26270; Beigelman *et al.,* U.S. Pat. No. 5,716,824; Usman *et al.,* U.S. Pat. No. 5,627,053; Woolf *et al.,* International PCT Publication No. WO 98/13526; Thompson *et al.,* USSN 60/082,404 which was filed on April 20, 1998; Karpeisky *et al.,* 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, *Biopolymers (Nucleic Acid Sciences),* 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.,* 67, 99-134; and Burlina *et al.,* 1997, *Bioorg. Med. Chem.,* 5, 1999-2010; all of the references are hereby incorporated in their totality by reference herein). Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of such teachings, similar modifications can be used as described herein to modify

the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi is cells is not significantly inhibited.

While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorodithioate, and/or 5'-methylphosphonate linkages improves stability, excessive modifications can cause some toxicity or decreased activity. Therefore, when designing nucleic acid molecules, the amount of these internucleotide linkages should be minimized. The reduction in the concentration of these linkages should lower toxicity, resulting in increased efficacy and higher specificity of these molecules.

Short interfering nucleic acid (siNA) molecules having chemical modifications that maintain or enhance activity are provided. Such a nucleic acid is also generally more resistant to nucleases than an unmodified nucleic acid. Accordingly, the *in vitro* and/or *in vivo* activity should not be significantly lowered. In cases in which modulation is the goal, therapeutic nucleic acid molecules delivered exogenously should optimally be stable within cells until translation of the target RNA has been modulated long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Improvements in the chemical synthesis of RNA and DNA (Wincott *et al.,* 1995, *Nucleic Acids Res.* 23, 2677; Caruthers *et al.,* 1992, *Methods in Enzymology* 211,3-19 (incorporated by reference herein)) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability, as described above.

In one embodiment, nucleic acid molecules of the invention include one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein the modifications confer the ability to hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J. Am. Chem. Soc.,* 120, 8531-8532. A single G-clamp analog substitution within an oligonucleotide can result in substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in nucleic acid molecules of the invention results in both enhanced affinity and specificity to nucleic acid targets, complementary sequences, or template strands. In another

embodiment, nucleic acid molecules of the invention include one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) LNA "locked nucleic acid" nucleotides such as a 2', 4'-C methylene bicyclo nucleotide (see for example Wengel *et al.*, International PCT Publication No. WO 00/66604 and WO 99/14226).

In another embodiment, the invention features conjugates and/or complexes of siNA molecules of the invention. Such conjugates and/or complexes can be used to facilitate delivery of siNA molecules into a biological system, such as a cell. The conjugates and complexes provided by the instant invention can impart therapeutic activity by transferring therapeutic compounds across cellular membranes, altering the pharmacokinetics, and/or modulating the localization of nucleic acid molecules of the invention. The present invention encompasses the design and synthesis of novel conjugates and complexes for the delivery of molecules, including, but not limited to, small molecules, lipids, cholesterol, phospholipids, nucleosides, nucleotides, nucleic acids, antibodies, toxins, negatively charged polymers and other polymers, for example proteins, peptides, hormones, carbohydrates, polyethylene glycols, or polyamines, across cellular membranes. In general, the transporters described are designed to be used either individually or as part of a multi-component system, with or without degradable linkers. These compounds are expected to improve delivery and/or localization of nucleic acid molecules of the invention into a number of cell types originating from different tissues, in the presence or absence of serum (see Sullenger and Cech, U.S. Pat. No. 5,854,038). Conjugates of the molecules described herein can be attached to biologically active molecules via linkers that are biodegradable, such as biodegradable nucleic acid linker molecules.

The term "biodegradable linker" as used herein, refers to a nucleic acid or non-nucleic acid linker molecule that is designed as a biodegradable linker to connect one molecule to another molecule, for example, a biologically active molecule to a siNA molecule of the invention or the sense and antisense strands of a siNA molecule of the invention. The biodegradable linker is designed such that its stability can be modulated for a particular purpose, such as delivery to a particular tissue or cell type. The stability of a nucleic acid-based biodegradable linker molecule can be modulated by using various chemistries, for example combinations of ribonucleotides, deoxyribonucleotides, and

chemically-modified nucleotides, such as 2'-O-methyl, 2'-fluoro, 2'-amino, 2'-O-amino, 2'-C-allyl, 2'-O-allyl, and other 2'-modified or base modified nucleotides. The biodegradable nucleic acid linker molecule can be a dimer, trimer, tetramer or longer nucleic acid molecule, for example, an oligonucleotide of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length, or can comprise a single nucleotide with a phosphorus-based linkage, for example, a phosphoramidate or phosphodiester linkage. The biodegradable nucleic acid linker molecule can also comprise nucleic acid backbone, nucleic acid sugar, or nucleic acid base modifications.

The term "biodegradable" as used herein, refers to degradation in a biological system, for example enzymatic degradation or chemical degradation.

The term "biologically active molecule" as used herein, refers to compounds or molecules that are capable of eliciting or modifying a biological response in a system. Non-limiting examples of biologically active siNA molecules either alone or in combination with other molecules contemplated by the instant invention include therapeutically active molecules such as antibodies, cholesterol, hormones, antivirals, peptides, proteins, chemotherapeutics, small molecules, vitamins, co-factors, nucleosides, nucleotides, oligonucleotides, enzymatic nucleic acids, antisense nucleic acids, triplex forming oligonucleotides, 2,5-A chimeras, siNA, dsRNA, allozymes, aptamers, decoys and analogs thereof. Biologically active molecules of the invention also include molecules capable of modulating the pharmacokinetics and/or pharmacodynamics of other biologically active molecules, for example, lipids and polymers such as polyamines, polyamides, polyethylene glycol and other polyethers.

The term "phospholipid" as used herein, refers to a hydrophobic molecule comprising at least one phosphorus group. For example, a phospholipid can comprise a phosphorus-containing group and saturated or unsaturated alkyl group, optionally substituted with OH, COOH, oxo, amine, or substituted or unsubstituted aryl groups.

Therapeutic nucleic acid molecules (*e.g.*, siNA molecules) delivered exogenously optimally are stable within cells until reverse transcription of the RNA has been modulated long enough to reduce the levels of the RNA transcript. The nucleic acid molecules are resistant to nucleases in order to function as effective intracellular

therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

In yet another embodiment, siNA molecules having chemical modifications that maintain or enhance enzymatic activity of proteins involved in RNAi are provided. Such nucleic acids are also generally more resistant to nucleases than unmodified nucleic acids. Thus, *in vitro* and/or *in vivo* the activity should not be significantly lowered.

Use of the nucleic acid-based molecules of the invention will lead to better treatment of the disease progression by affording the possibility of combination therapies (*e.g.*, multiple siNA molecules targeted to different genes; nucleic acid molecules coupled with known small molecule modulators; or intermittent treatment with combinations of molecules, including different motifs and/or other chemical or biological molecules). The treatment of subjects with siNA molecules can also include combinations of different types of nucleic acid molecules, such as enzymatic nucleic acid molecules (ribozymes), allozymes, antisense, 2,5-A oligoadenylate, decoys, and aptamers.

In another aspect a siNA molecule of the invention comprises one or more 5' and/or a 3'- cap structure, for example on only the sense siNA strand, the antisense siNA strand, or both siNA strands.

By "cap structure" is meant chemical modifications, which have been incorporated at either terminus of the oligonucleotide (see, for example, Adamic *et al.*, U.S. Pat. No. 5,998,203, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and may help in delivery and/or localization within a cell. The cap may be present at the 5'-terminus (5'-cap) or at the 3'-terminal (3'-cap) or may be present on both termini. In non-limiting examples, the 5'-cap includes, but is not limited to, glyceryl, inverted deoxy abasic residue (moiety); 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide, 4'-thio nucleotide; carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; *threo*-pentofuranosyl nucleotide;

acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety.

Non-limiting examples of the 3'-cap include, but are not limited to, glyceryl, inverted deoxy abasic residue (moiety), 4', 5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate; 3-aminopropyl phosphate; 6-aminohexyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; phosphorodithioate; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer, 1993, *Tetrahedron* 49, 1925; incorporated by reference herein).

By the term "non-nucleotide" is meant any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine and therefore lacks a base at the 1'-position.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkyl group can be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino, or SH. The term also includes alkenyl groups that are unsaturated hydrocarbon

groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons. More preferably, it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, $N(CH_3)_2$, amino, or SH. The term "alkyl" also includes alkynyl groups that have an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably, it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino or SH.

Such alkyl groups can also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group that has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above). Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An "amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alkylaryl or hydrogen. An "ester" refers to an -C(O)-OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

By "nucleotide" as used herein is as recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the

sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see, for example, Usman and McSwiggen, *supra*; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, *supra,* all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, *Nucleic Acids Res.* 22, 2183. Some of the non-limiting examples of base modifications that can be introduced into nucleic acid molecules include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (*e.g.*, 5-methylcytidine), 5-alkyluridines (*e.g.*, ribothymidine), 5-halouridine (*e.g.*, 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (*e.g.* 6-methyluridine), propyne, and others (Burgin *et al.*, 1996, *Biochemistry*, 35, 14090; Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents.

In one embodiment, the invention features modified siNA molecules, with phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, phosphotriester, morpholino, amidate carbamate, carboxymethyl, acetamidate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions. For a review of oligonucleotide backbone modifications, see Hunziker and Leumann, 1995, *Nucleic Acid Analogues: Synthesis and Properties,* in *Modern Synthetic Methods,* VCH, 331-417, and Mesmaeker *et al.*, 1994, *Novel Backbone Replacements for Oligonucleotides,* in *Carbohydrate Modifications in Antisense Research,* ACS, 24-39.

By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position, see for example Adamic *et al.*, U.S. Pat. No. 5,998,203.

By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, thymine, or uracil joined to the 1' carbon of β-D-ribo-furanose.

By "modified nucleoside" is meant any nucleotide base which contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate. Non-limiting examples of modified nucleotides are shown by Formulae I-VII and/or other modifications described herein.

In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH_2 or 2'-*O*- NH_2, which can be modified or unmodified. Such modified groups are described, for example, in Eckstein *et al.,* U.S. Pat. No. 5,672,695 and Matulic-Adamic *et al.,* U.S. Pat. No. 6,248,878, which are both incorporated by reference in their entireties.

Various modifications to nucleic acid siNA structure can be made to enhance the utility of these molecules. Such modifications will enhance shelf-life, half-life *in vitro,* stability, and ease of introduction of such oligonucleotides to the target site, *e.g.,* to enhance penetration of cellular membranes, and confer the ability to recognize and bind to targeted cells.

Administration of Nucleic Acid Molecules

A siNA molecule of the invention can be adapted for use to treat, for example, Huntinton disease and related conditions such as progressive chorea, rigidity, dementia, and seizures, spinocerebellar ataxia, spinal and bulbar muscular dystrophy (SBMA), dentatorubropallidoluysian atrophy (DRPLA) and any other diseases or conditions that are related to or will respond to the levels of a repeat expansion (RE) gene in a cell or tissue, alone or in combination with other therapies. For example, a siNA molecule can comprise a delivery vehicle, including liposomes, for administration to a subject, carriers and diluents and their salts, and/or can be present in pharmaceutically acceptable formulations. Methods for the delivery of nucleic acid molecules are described in Akhtar *et al.,* 1992, *Trends Cell Bio.*, 2, 139; *Delivery Strategies for Antisense Oligonucleotide Therapeutics*, ed. Akhtar, 1995, Maurer *et al.,* 1999, *Mol. Membr. Biol.,* 16, 129-140; Hofland and Huang, 1999, *Handb. Exp. Pharmacol.,* 137, 165-192; and Lee *et al.,* 2000, *ACS Symp. Ser.,* 752, 184-192, all of which are incorporated herein by reference. Beigelman *et al.,* U.S. Pat. No. 6,395,713 and Sullivan *et al.,* PCT WO 94/02595 further describe the general methods for delivery of nucleic acid molecules.

These protocols can be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules can be administered to cells by a variety of methods known to those of skill in the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as biodegradable polymers, hydrogels, cyclodextrins (see for example Gonzalez *et al.,* 1999, *Bioconjugate Chem.,* 10, 1068-1074; Wang *et al.,* International PCT publication Nos. WO 03/47518 and WO 03/46185), poly(lactic-co-glycolic)acid (PLGA) and PLCA microspheres (see for example US Patent 6,447,796 and US Patent Application Publication No. US 2002130430), biodegradable nanocapsules, and bioadhesive microspheres, or by proteinaceous vectors (O'Hare and Normand, International PCT Publication No. WO 00/53722). In another embodiment, the nucleic acid molecules of the invention can also be formulated or complexed with polyethyleneimine and derivatives thereof, such as polyethyleneimine-polyethyleneglycol-N-acetylgalactosamine (PEI-PEG-GAL) or polyethyleneimine-polyethyleneglycol-tri-N-acetylgalactosamine (PEI-PEG-triGAL) derivatives. Alternatively, the nucleic acid/vehicle combination is locally delivered by direct injection or by use of an infusion pump. Many examples in the art describe CNS delivery methods of oligonucleotides by osmotic pump, (see Chun *et al.,* 1998, *Neuroscience Letters,* 257, 135-138, D'Aldin *et al.,* 1998, *Mol. Brain Research,* 55, 151-164, Dryden *et al.,* 1998, *J. Endocrinol.,* 157, 169-175, Ghirnikar *et al.,* 1998, *Neuroscience Letters,* 247, 21-24) or direct infusion (Broaddus *et al.,* 1997, *Neurosurg. Focus,* 3, article 4). Various devices as are known in the art can be utilized to deliver nucleic acid molecules of the invention (see for example Turner, 2003, *Acta Neurochir Suppl.,* 87, 29-35). Other routes of delivery include, but are not limited to oral (tablet or pill form) and/or intrathecal delivery (Gold, 1997, *Neuroscience,* 76, 1153-1158). For a comprehensive review on drug delivery strategies including broad coverage of CNS delivery, see Ho *et al.,* 1999, *Curr. Opin. Mol. Ther.,* 1, 336-343 and Jain, *Drug Delivery Systems: Technologies and Commercial Opportunities,* Decision Resources, 1998 and Groothuis *et al.,* 1997, *J. NeuroVirol.,* 3, 387-400. Direct injection of the nucleic acid molecules of the invention, whether subcutaneous, intramuscular, or intradermal, can take place using standard needle and syringe methodologies, or by needle-free technologies such as those described in Conry *et al.,* 1999, *Clin. Cancer Res.,* 5, 2330-2337 and Barry *et al.,* International PCT Publication No. WO 99/31262. The molecules

of the instant invention can be used as pharmaceutical agents. Pharmaceutical agents prevent, modulate the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state in a subject.

Experiments have demonstrated the efficient *in vivo* uptake of nucleic acids by neurons. As an example of local administration of nucleic acids to nerve cells, Sommer *et al.*, 1998, *Antisense Nuc. Acid Drug Dev.*, 8, 75, describe a study in which a 15mer phosphorothioate antisense nucleic acid molecule to c-fos is administered to rats via microinjection into the brain. Antisense molecules labeled with tetramethylrhodamine-isothiocyanate (TRITC) or fluorescein isothiocyanate (FITC) were taken up by exclusively by neurons thirty minutes post-injection. A diffuse cytoplasmic staining and nuclear staining was observed in these cells. As an example of systemic administration of nucleic acid to nerve cells, Epa *et al.*, 2000, *Antisense Nuc. Acid Drug Dev.*, 10, 469, describe an *in vivo* mouse study in which beta-cyclodextrin-adamantane-oligonucleotide conjugates were used to target the p75 neurotrophin receptor in neuronally differentiated PC12 cells. Following a two week course of IP administration, pronounced uptake of p75 neurotrophin receptor antisense was observed in dorsal root ganglion (DRG) cells. In addition, a marked and consistent down-regulation of p75 was observed in DRG neurons. Additional approaches to the targeting of nucleic acid to neurons are described in Broaddus *et al.*, 1998, *J. Neurosurg.*, 88(4), 734; Karle *et al.*, 1997, *Eur. J. Pharmocol.*, 340(2/3), 153; Bannai *et al.*, 1998, *Brain Research,* 784(1,2), 304; Rajakumar *et al.*, 1997, *Synapse*, 26(3), 199; Wu-pong *et al.*, 1999, *BioPharm*, 12(1), 32; Bannai *et al.*, 1998, *Brain Res. Protoc.*, 3(1), 83; Simantov *et al.*, 1996, *Neuroscience,* 74(1), 39. Nucleic acid molecules of the invention are therefore amenable to delivery to and uptake by cells that express repeat expansion allelic variants for modulation of RE gene expression.

The delivery of nucleic acid molecules of the invention, targeting RE is provided by a variety of different strategies. Traditional approaches to CNS delivery that can be used include, but are not limited to, intrathecal and intracerebroventricular administration, implantation of catheters and pumps, direct injection or perfusion at the site of injury or lesion, injection into the brain arterial system, or by chemical or osmotic opening of the blood-brain barrier. Other approaches can include the use of various

transport and carrier systems, for example though the use of conjugates and biodegradable polymers. Furthermore, gene therapy approaches, for example as described in Kaplitt *et al.*, US 6,180,613 and Davidson, WO 04/013280, can be used to express nucleic acid molecules in the CNS.

In one embodiment, a siNA molecule of the invention is complexed with membrane disruptive agents such as those described in U.S. Patent Appliaction Publication No. 20010007666, incorporated by reference herein in its entirety including the drawings. In another embodiment, the membrane disruptive agent or agents and the siNA molecule are also complexed with a cationic lipid or helper lipid molecule, such as those lipids described in U.S. Patent No. 6,235,310, incorporated by reference herein in its entirety including the drawings.

Thus, the invention features a pharmaceutical composition comprising one or more nucleic acid(s) of the invention in an acceptable carrier, such as a stabilizer, buffer, and the like. The polynucleotides of the invention can be administered (*e.g.*, RNA, DNA or protein) and introduced into a subject by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions, suspensions for injectable administration, and the other compositions known in the art.

The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic administration, into a cell or subject, including for example a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell (*i.e.*, a cell

to which the negatively charged nucleic acid is desirable for delivery). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms that prevent the composition or formulation from exerting its effect.

By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes that lead to systemic absorption include, without limitation: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes exposes the siNA molecules of the invention to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation that can facilitate the association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach can provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells, such as cells producing excess repeat expansion genes.

By "pharmaceutically acceptable formulation" is meant, a composition or formulation that allows for the effective distribution of the nucleic acid molecules of the instant invention in the physical location most suitable for their desired activity. Non-limiting examples of agents suitable for formulation with the nucleic acid molecules of the instant invention include: P-glycoprotein inhibitors (such as Pluronic P85), which can enhance entry of drugs into the CNS (Jolliet-Riant and Tillement, 1999, *Fundam. Clin. Pharmacol.*, 13, 16-26); biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery after intracerebral implantation (Emerich, DF *et al*, 1999, *Cell Transplant*, 8, 47-58) (Alkermes, Inc. Cambridge, MA); and loaded nanoparticles, such as those made of polybutylcyanoacrylate, which can deliver drugs across the blood brain barrier and can alter neuronal uptake mechanisms (*Prog Neuropsychopharmacol Biol Psychiatry*, 23, 941-949, 1999). Other non-limiting examples of delivery strategies for the nucleic acid molecules of the instant invention

include material described in Boado *et al.*, 1998, *J. Pharm. Sci.*, 87, 1308-1315; Tyler *et al.*, 1999, *FEBS Lett.*, 421, 280-284; Pardridge *et al.*, 1995, *PNAS USA.*, 92, 5592-5596; Boado, 1995, *Adv. Drug Delivery Rev.*, 15, 73-107; Aldrian-Herrada *et al.*, 1998, *Nucleic Acids Res.*, 26, 4910-4916; and Tyler *et al.*, 1999, *PNAS USA.*, 96, 7053-7058.

The invention also features the use of the composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-circulating liposomes or stealth liposomes). These formulations offer a method for increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al. Chem. Rev.* 1995, 95, 2601-2627; Ishiwata *et al., Chem. Pharm. Bull.* 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al., Science* 1995, 267, 1275-1276; Oku *et al.*,1995, *Biochim. Biophys. Acta*, 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu *et al., J. Biol. Chem.* 1995, 42, 24864-24870; Choi *et al.*, International PCT Publication No. WO 96/10391; Ansell *et al.*, International PCT Publication No. WO 96/10390; Holland *et al.*, International PCT Publication No. WO 96/10392). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid accumulation in metabolically aggressive MPS tissues such as the liver and spleen.

The present invention also includes compositions prepared for storage or administration that include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985), hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include

sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors that those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

The nucleic acid molecules of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (*e.g.*, intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a nucleic acid molecule of the invention and a pharmaceutically acceptable carrier. One or more nucleic acid molecules of the invention can be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing nucleic acid molecules of the invention can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be, for example, inert diluents; such as calcium carbonate, sodium

carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring

agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The nucleic acid molecules of the invention can also be administered in the form of suppositories, *e.g.*, for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per subject per day). The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

It is understood that the specific dose level for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

The nucleic acid molecules of the present invention can also be administered to a subject in combination with other therapeutic compounds to increase the overall

therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

In one embodiment, the invention comprises compositions suitable for administering nucleic acid molecules of the invention to specific cell types. For example, the asialoglycoprotein receptor (ASGPr) (Wu and Wu, 1987, *J. Biol. Chem.* 262, 4429-4432) is unique to hepatocytes and binds branched galactose-terminal glycoproteins, such as asialoorosomucoid (ASOR). In another example, the folate receptor is overexpressed in many cancer cells. Binding of such glycoproteins, synthetic glycoconjugates, or folates to the receptor takes place with an affinity that strongly depends on the degree of branching of the oligosaccharide chain, for example, triatennary structures are bound with greater affinity than biatenarry or monoatennary chains (Baenziger and Fiete, 1980, *Cell,* 22, 611-620; Connolly *et al.,* 1982, *J. Biol. Chem.,* 257, 939-945). Lee and Lee, 1987, *Glycoconjugate J.*, 4, 317-328, obtained this high specificity through the use of N-acetyl-D-galactosamine as the carbohydrate moiety, which has higher affinity for the receptor, compared to galactose. This "clustering effect" has also been described for the binding and uptake of mannosyl-terminating glycoproteins or glycoconjugates (Ponpipom *et al.,* 1981, *J. Med. Chem.,* 24, 1388-1395). The use of galactose, galactosamine, or folate based conjugates to transport exogenous compounds across cell membranes can provide a targeted delivery approach to, for example, the treatment of liver disease, cancers of the liver, or other cancers. The use of bioconjugates can also provide a reduction in the required dose of therapeutic compounds required for treatment. Furthermore, therapeutic bioavialability, pharmacodynamics, and pharmacokinetic parameters can be modulated through the use of nucleic acid bioconjugates of the invention. Non-limiting examples of such bioconjugates are described in Vargeese *et al.,* USSN 10/201,394, filed August 13, 2001; and Matulic-Adamic *et al.,* USSN 10/151,116, filed May 17, 2002. In one embodiment, nucleic acid molecules of the invention are complexed with or covalently attached to nanoparticles, such as Hepatitis B virus S, M, or L evelope proteins (see for example Yamado *et al.,* 2003, *Nature Biotechnology*, 21, 885). In one embodiment, nucleic acid molecules of the invention are delivered with specificity for human tumor cells, specifically non-apoptotic human tumor cells including for example T-cells, hepatocytes, breast carcinoma cells, ovarian carcinoma cells, melanoma cells, intestinal epithelial

cells, prostate cells, testicular cells, non-small cell lung cancers, small cell lung cancers, etc.

Alternatively, certain siNA molecules of the instant invention can be expressed within cells from eukaryotic promoters (*e.g.*, Izant and Weintraub, 1985, *Science,* 229, 345; McGarry and Lindquist, 1986, *Proc. Natl. Acad. Sci.*, USA 83, 399; Scanlon *et al.*, 1991, *Proc. Natl. Acad. Sci. USA*, 88, 10591-5; Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Dropulic *et al.*, 1992, *J. Virol.*, 66, 1432-41; Weerasinghe *et al.*, 1991, *J. Virol.*, 65, 5531-4; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. USA*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Sarver *et al.*, 1990 *Science,* 247, 1222-1225; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Good *et al.*, 1997, *Gene Therapy*, 4, 45. Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a enzymatic nucleic acid (Draper *et al.*, PCT WO 93/23569, and Sullivan *et al.*, PCT WO 94/02595; Ohkawa *et al.*, 1992, *Nucleic Acids Symp. Ser.*, 27, 15-6; Taira *et al.*, 1991, *Nucleic Acids Res.*, 19, 5125-30; Ventura *et al.*, 1993, *Nucleic Acids Res.*, 21, 3249-55; Chowrira *et al.*, 1994, *J. Biol. Chem.*, 269, 25856.

In another aspect of the invention, RNA molecules of the present invention can be expressed from transcription units (see for example Couture *et al.*, 1996, *TIG.*, 12, 510) inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. In another embodiment, pol III based constructs are used to express nucleic acid molecules of the invention (see for example Thompson, U.S. Pats. Nos. 5,902,880 and 6,146,886). The recombinant vectors capable of expressing the siNA molecules can be delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecule interacts with the target mRNA and generates an RNAi response. Delivery of siNA molecule expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into

the subject, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.*, 1996, *TIG.*, 12, 510).

In one aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the instant invention. The expression vector can encode one or both strands of a siNA duplex, or a single self-complementary strand that self hybridizes into a siNA duplex. The nucleic acid sequences encoding the siNA molecules of the instant invention can be operably linked in a manner that allows expression of the siNA molecule (see for example Paul *et al.*, 2002, *Nature Biotechnology,* 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology,* 19, 497; Lee *et al.*, 2002, *Nature Biotechnology,* 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online publication doi:10.1038/nm725).

In another aspect, the invention features an expression vector comprising: a) a transcription initiation region (*e.g.*, eukaryotic pol I, II or III initiation region); b) a transcription termination region (*e.g.*, eukaryotic pol I, II or III termination region); and c) a nucleic acid sequence encoding at least one of the siNA molecules of the instant invention,wherein said sequence is operably linked to said initiation region and said termination region in a manner that allows expression and/or delivery of the siNA molecule. The vector can optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the siNA of the invention; and/or an intron (intervening sequences).

Transcription of the siNA molecule sequences can be driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters are expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type depends on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, *Proc. Natl. Acad. Sci. U S A*, 87, 6743-7; Gao and Huang 1993, *Nucleic Acids Res.*, 21, 2867-72; Lieber *et al.*, 1993, *Methods Enzymol.*, 217, 47-66; Zhou *et al.*, 1990, *Mol. Cell. Biol.*, 10, 4529-37). Several investigators have demonstrated that nucleic acid molecules expressed from such promoters can function in mammalian cells (e.g.

Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. U S A*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Yu *et al.*, 1993, *Proc. Natl. Acad. Sci. U S A*, 90, 6340-4; L'Huillier *et al.*, 1992, *EMBO J.*, 11, 4411-8; Lisziewicz *et al.*, 1993, *Proc. Natl. Acad. Sci. U. S. A*, 90, 8000-4; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Sullenger & Cech, 1993, *Science,* 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as siNA in cells (Thompson *et al., supra*; Couture and Stinchcomb, *1996, supra*; Noonberg *et al.*, 1994, *Nucleic Acid Res.*, 22, 2830; Noonberg *et al.*, U.S. Pat. No. 5,624,803; Good *et al.*, 1997, *Gene Ther.*, 4, 45; Beigelman *et al.*, International PCT Publication No. WO 96/18736. The above siNA transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, *1996, supra).*

In another aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the siNA molecules of the invention in a manner that allows expression of that siNA molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; and c) a nucleic acid sequence encoding at least one strand of the siNA molecule, wherein the sequence is operably linked to the initiation region and the termination region in a manner that allows expression and/or delivery of the siNA molecule.

In another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; and d) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the open reading frame and the termination region in a manner that allows expression and/or delivery of the siNA molecule. In yet another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; and d) a

nucleic acid sequence encoding at least one siNA molecule, wherein the sequence is operably linked to the initiation region, the intron and the termination region in a manner which allows expression and/or delivery of the nucleic acid molecule.

In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; and e) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the intron, the open reading frame and the termination region in a manner which allows expression and/or delivery of the siNA molecule.

Huntingtin biology and biochemistry

The following discussion is adapted from the Revilla *et al.,* 2002, Huntington Disease, Copyright 2004, eMedicine.com, Inc. and the OMIM database entry for Huntington disease, Copyright © 1966-2004 Johns Hopkins University. Huntington disease (HD) is an incurable, adult-onset, autosomal dominant inherited disorder associated with cell loss within a specific subset of neurons in the basal ganglia and cortex. HD is named after George Huntington, the physician who described it as hereditary chorea in 1872. Characteristic features of HD include involuntary movements, dementia, and behavioral changes. Huntington disease (HD) is inherited as an autosomal dominant disease that gives rise to progressive, selective or localized neural cell death associated with choreic movements and dementia. The classic signs of Huntington disease are progressive chorea, rigidity, and dementia, oftem associated with seizures. A characteristic atrophy of the caudate nucleus is seen in radiographic images. The most striking neuropathology in HD occurs within the neostriatum, in which gross atrophy of the caudate nucleus and putamen is accompanied by selective neuronal loss and astrogliosis. Other regions, including the globus pallidus, thalamus, subthalamic nucleus, substantia nigra, and cerebellum, show varying degrees of atrophy depending on the pathologic grade. The extent of gross striatal pathology, neuronal loss, and gliosis provides a basis for grading the severity of HD pathology (grades 0-4). Typically, there is a prodromal phase of mild psychotic and behavioral symptoms which precedes frank Huntington chorea by up to 10 years.

The disease is associated with increases in the length of a polyglutamine or CAG triplet repeat present in the Huntingtin gene located on chromosome 4p16.3. The function of huntingtin is not known. Normally, it is located in the cytoplasm. The association of huntingtin with the cytoplasmic surface of a variety of organelles, including transport vesicles, synaptic vesicles, microtubules, and mitochondria, raises the possibility of the occurrence of normal cellular interactions that might be relevant to neurodegeneration. Although the variation in age at onset of HD is partly explained by the size of the expanded CAG repeat, it is strongly heritable, which suggests that other genes modify the age at onset.

Studies have shown that mutant huntingtin protein from human brain, transgenic animals, and cells is more resistant to proteolysis than normal huntingtin. The N-terminal cleavage fragments that arise from the processing of normal huntingtin are sequestered by full-length huntingtin. One model has been proposed in which inhibition of proteolysis of mutant huntingtin leads to aggregation and neurotoxicity through the sequestration of important targets, including normal huntingtin. The presence of neuronal intranuclear inclusions (NIIs) initially led to the view that they are toxic and, hence, pathogenic. More recent data from striatal neuronal cultures transfected with mutant huntingtin and transgenic mice carrying the spinocerebellar ataxia-1 (*SCA-1*) gene (another CAG repeat disorder) suggest that NIIs may not be necessary or sufficient to cause neuronal cell death, but translocation into the nucleus is sufficient to cause neuronal cell death. Caspase inhibition in clonal striatal cells showed no correlation between the reduction of aggregates in the cells and increased survival.

Cytoplasmic protein extracts from several rat brain regions, including striatum and cortex (sites of neuronal degeneration in HD), contain a 63 kD RNA-binding protein that interacts specifically with CAG repeat sequences. It has been noted that the protein RNA interactions are dependent upon the length of the CAG repeat, and that longer repeats bind substantially more protein. Two CAG binding proteins have been identified in human cortex and striatum, one of 63 kD and another of 49 kD. These data suggest mechanisms by which RNA binding proteins may be involved in the pathological course of trinucleotide-associated neurologic diseases (see for example McLaughlin *et al.,* 1996, *Hum. Genet.* 59, 561-569.

The Huntington's Disease Collaborative Research Group (1993, *Cell,* 72, 971-983) found a gene, designated IT15 (important transcript 15) and later called huntingtin, which was isolated using cloned trapped exons and which contains a polymorphic trinucleotide repeat that is expanded and unstable on HD chromosomes. A (CAG)n repeat longer than the normal range was observed on HD chromosomes from all disease families examined. The families came from a variety of ethnic backgrounds and demonstrated a variety of 4p16.3 haplotypes. The (CAG)n repeat appeared to be located within the coding sequence of a predicted protein of about 348 kD that is widely expressed but unrelated to any known gene. Thus, the HD mutation involves an unstable DNA segment similar to those previously observed in several disorders, including the fragile X syndrome, Kennedy syndrome, and myotonic dystrophy. The fact that the phenotype of HD is completely dominant suggests that the disorder results from a gain-of-function mutation in which either the mRNA product or the protein product of the disease allele has some new property or is expressed inappropriately (see for example, Myers *et al.,* 1989, *Am. J. Hum. Genet.,* 34, 481-488).

The use of small interfering nucleic acid molecules targeting HD, for example mutant alleles associated with Huntington disease, provides a class of novel therapeutic agents that can be used in the the treatment of Huntington Disease and any other disease or condition that responds to modulation of HD genes.

Examples:

The following are non-limiting examples showing the selection, isolation, synthesis and activity of nucleic acids of the instant invention.

Example 1: Tandem synthesis of siNA constructs

Exemplary siNA molecules of the invention are synthesized in tandem using a cleavable linker, for example, a succinyl-based linker. Tandem synthesis as described herein is followed by a one-step purification process that provides RNAi molecules in high yield. This approach is highly amenable to siNA synthesis in support of high throughput RNAi screening, and can be readily adapted to multi-column or multi-well synthesis platforms.

After completing a tandem synthesis of a siNA oligo and its complement in which the 5'-terminal dimethoxytrityl (5'-O-DMT) group remains intact (trityl on synthesis), the oligonucleotides are deprotected as described above. Following deprotection, the siNA sequence strands are allowed to spontaneously hybridize. This hybridization yields a duplex in which one strand has retained the 5'-O-DMT group while the complementary strand comprises a terminal 5'-hydroxyl. The newly formed duplex behaves as a single molecule during routine solid-phase extraction purification (Trityl-On purification) even though only one molecule has a dimethoxytrityl group. Because the strands form a stable duplex, this dimethoxytrityl group (or an equivalent group, such as other trityl groups or other hydrophobic moieties) is all that is required to purify the pair of oligos, for example, by using a C18 cartridge.

Standard phosphoramidite synthesis chemistry is used up to the point of introducing a tandem linker, such as an inverted deoxy abasic succinate or glyceryl succinate linker (see **Figure 1**) or an equivalent cleavable linker. A non-limiting example of linker coupling conditions that can be used includes a hindered base such as diisopropylethylamine (DIPA) and/or DMAP in the presence of an activator reagent such as Bromotripyrrolidinophosphoniumhexaflurorophosphate (PyBrOP). After the linker is coupled, standard synthesis chemistry is utilized to complete synthesis of the second sequence leaving the terminal the 5'-O-DMT intact. Following synthesis, the resulting oligonucleotide is deprotected according to the procedures described herein and quenched with a suitable buffer, for example with 50mM NaOAc or 1.5M $NH_4H_2CO_3$.

Purification of the siNA duplex can be readily accomplished using solid phase extraction, for example using a Waters C18 SepPak 1g cartridge conditioned with 1 column volume (CV) of acetonitrile, 2 CV H2O, and 2 CV 50mM NaOAc. The sample is loaded and then washed with 1 CV H2O or 50mM NaOAc. Failure sequences are eluted with 1 CV 14% ACN (Aqueous with 50mM NaOAc and 50mM NaCl). The column is then washed, for example with 1 CV H2O followed by on-column detritylation, for example by passing 1 CV of 1% aqueous trifluoroacetic acid (TFA) over the column, then adding a second CV of 1% aqueous TFA to the column and allowing to stand for approximately 10 minutes. The remaining TFA solution is removed and the column washed with H20 followed by 1 CV 1M NaCl and additional

H2O. The siNA duplex product is then eluted, for example, using 1 CV 20% aqueous CAN.

Figure 2 provides an example of MALDI-TOF mass spectrometry analysis of a purified siNA construct in which each peak corresponds to the calculated mass of an individual siNA strand of the siNA duplex. The same purified siNA provides three peaks when analyzed by capillary gel electrophoresis (CGE), one peak presumably corresponding to the duplex siNA, and two peaks presumably corresponding to the separate siNA sequence strands. Ion exchange HPLC analysis of the same siNA contract only shows a single peak. Testing of the purified siNA construct using a luciferase reporter assay described below demonstrated the same RNAi activity compared to siNA constructs generated from separately synthesized oligonucleotide sequence strands.

Example 2: Identification of potential siNA target sites in any RNA sequence

The sequence of an RNA target of interest, such as a viral or human mRNA transcript, is screened for target sites, for example by using a computer folding algorithm. In a non-limiting example, the sequence of a gene or RNA gene transcript derived from a database, such as Genbank, is used to generate siNA targets having complementarity to the target. Such sequences can be obtained from a database, or can be determined experimentally as known in the art. Target sites that are known, for example, those target sites determined to be effective target sites based on studies with other nucleic acid molecules, for example ribozymes or antisense, or those targets known to be associated with a disease or condition such as those sites containing mutations or deletions, can be used to design siNA molecules targeting those sites. Various parameters can be used to determine which sites are the most suitable target sites within the target RNA sequence. These parameters include but are not limited to secondary or tertiary RNA structure, the nucleotide base composition of the target sequence, the degree of homology between various regions of the target sequence, or the relative position of the target sequence within the RNA transcript. Based on these determinations, any number of target sites within the RNA transcript can be chosen to screen siNA molecules for efficacy, for example by using *in vitro* RNA cleavage assays, cell culture, or animal models. In a non-limiting example, anywhere from 1 to 1000 target sites are chosen within the transcript based on the size of the siNA construct to be

used. High throughput screening assays can be developed for screening siNA molecules using methods known in the art, such as with multi-well or multi-plate assays to determine efficient reduction in target gene expression.

Example 3: Selection of siNA molecule target sites in a RNA

The following non-limiting steps can be used to carry out the selection of siNAs targeting a given gene sequence or transcript.

1. The target sequence is parsed *in silico* into a list of all fragments or subsequences of a particular length, for example 23 nucleotide fragments, contained within the target sequence. This step is typically carried out using a custom Perl script, but commercial sequence analysis programs such as Oligo, MacVector, or the GCG Wisconsin Package can be employed as well.

2. In some instances the siNAs correspond to more than one target sequence; such would be the case for example in targeting different transcripts of the same gene, targeting different transcripts of more than one gene, or for targeting both the human gene and an animal homolog. In this case, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find matching sequences in each list. The subsequences are then ranked according to the number of target sequences that contain the given subsequence; the goal is to find subsequences that are present in most or all of the target sequences. Alternately, the ranking can identify subsequences that are unique to a target sequence, such as a mutant target sequence. Such an approach would enable the use of siNA to target specifically the mutant sequence and not effect the expression of the normal sequence.

3. In some instances the siNA subsequences are absent in one or more sequences while present in the desired target sequence; such would be the case if the siNA targets a gene with a paralogous family member that is to remain untargeted. As in case 2 above, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find sequences that are present in the target gene but are absent in the untargeted paralog.

4. The ranked siNA subsequences can be further analyzed and ranked according to GC content. A preference can be given to sites containing 30-70% GC, with a further preference to sites containing 40-60% GC.

5. The ranked siNA subsequences can be further analyzed and ranked according to self-folding and internal hairpins. Weaker internal folds are preferred; strong hairpin structures are to be avoided.

6. The ranked siNA subsequences can be further analyzed and ranked according to whether they have runs of GGG or CCC in the sequence. GGG (or even more Gs) in either strand can make oligonucleotide synthesis problematic and can potentially interfere with RNAi activity, so it is avoided whenever better sequences are available. CCC is searched in the target strand because that will place GGG in the antisense strand.

7. The ranked siNA subsequences can be further analyzed and ranked according to whether they have the dinucleotide UU (uridine dinucleotide) on the 3'-end of the sequence, and/or AA on the 5'-end of the sequence (to yield 3' UU on the antisense sequence). These sequences allow one to design siNA molecules with terminal TT thymidine dinucleotides.

8. Four or five target sites are chosen from the ranked list of subsequences as described above. For example, in subsequences having 23 nucleotides, the right 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the upper (sense) strand of the siNA duplex, while the reverse complement of the left 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the lower (antisense) strand of the siNA duplex (see **Tables II and III**). If terminal TT residues are desired for the sequence (as described in paragraph 7), then the two 3' terminal nucleotides of both the sense and antisense strands are replaced by TT prior to synthesizing the oligos.

9. The siNA molecules are screened in an *in vitro*, cell culture or animal model system to identify the most active siNA molecule or the most preferred target site within the target RNA sequence.

10. Other design considerations can be used when selecting target nucleic acid sequences, see for example Reynolds *et al.*, 2004, *Nature Biotechnology Advanced Online Publication*, 1 February 2004, doi:10.1038/nbt936 and Ui-Tei et al., 2004, Nucleic Acids Research, 32, doi:10.1093/nar/gkh247.

In an alternate approach, a pool of siNA constructs specific to a HD target sequence is used to screen for target sites in cells expressing HD RNA, such as COS-1 cells (see for example Sittler *et al.*, 2001, *Human Molecular Genetics*, 10, 1307-1315). The general strategy used in this approach is shown in **Figure 9.** A non-limiting example of such is a pool comprising sequences having any of SEQ ID NOS 1-3577. Cells expressing HD (e.g., COS-1 or PC12 cells) are transfected with the pool of siNA constructs and cells that demonstrate a phenotype associated with HD inhibition are sorted. The pool of siNA constructs can be expressed from transcription cassettes inserted into appropriate vectors (see for example **Figure 7** and **Figure 8**). The siNA from cells demonstrating a positive phenotypic change (e.g., decreased proliferation, decreased HD mRNA levels or decreased HD protein expression), are sequenced to determine the most suitable target site(s) within the target HD RNA sequence.

Example 4: HD targeted siNA design

siNA target sites were chosen by analyzing sequences of the HD RNA target and optionally prioritizing the target sites on the basis of folding (structure of any given sequence analyzed to determine siNA accessibility to the target), by using a library of siNA molecules as described in Example 3, or alternately by using an *in vitro* siNA system as described in Example 6 herein. siNA molecules were designed that could bind each target and are optionally individually analyzed by computer folding to assess whether the siNA molecule can interact with the target sequence. Varying the length of the siNA molecules can be chosen to optimize activity. Generally, a sufficient number of complementary nucleotide bases are chosen to bind to, or otherwise interact with, the target RNA, but the degree of complementarity can be modulated to accommodate siNA duplexes or varying length or base composition. By using such methodologies, siNA molecules can be designed to target sites within any known RNA sequence, for example those RNA sequences corresponding to the any gene transcript.

Chemically modified siNA constructs are designed to provide nuclease stability for systemic administration in vivo and/or improved pharmacokinetic, localization, and delivery properties while preserving the ability to mediate RNAi activity. Chemical modifications as described herein are introduced synthetically using synthetic methods described herein and those generally known in the art. The synthetic siNA constructs are then assayed for nuclease stability in serum and/or cellular/tissue extracts (e.g. liver extracts). The synthetic siNA constructs are also tested in parallel for RNAi activity using an appropriate assay, such as a luciferase reporter assay as described herein or another suitable assay that can quantity RNAi activity. Synthetic siNA constructs that possess both nuclease stability and RNAi activity can be further modified and re-evaluated in stability and activity assays. The chemical modifications of the stabilized active siNA constructs can then be applied to any siNA sequence targeting any chosen RNA and used, for example, in target screening assays to pick lead siNA compounds for therapeutic development (see for example **Figure 11**).

Example 5: Chemical Synthesis and Purification of siNA

siNA molecules can be designed to interact with various sites in the RNA message, for example, target sequences within the RNA sequences described herein. The sequence of one strand of the siNA molecule(s) is complementary to the target site sequences described above. The siNA molecules can be chemically synthesized using methods described herein. Inactive siNA molecules that are used as control sequences can be synthesized by scrambling the sequence of the siNA molecules such that it is not complementary to the target sequence. Generally, siNA constructs can by synthesized using solid phase oligonucleotide synthesis methods as described herein (see for example Usman *et al.,* US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,117,657; 6,353,098; 6,362,323; 6,437,117; 6,469,158; Scaringe *et al.,* US Patent Nos. 6,111,086; 6,008,400; 6,111,086 all incorporated by reference herein in their entirety).

In a non-limiting example, RNA oligonucleotides are synthesized in a stepwise fashion using the phosphoramidite chemistry as is known in the art. Standard phosphoramidite chemistry involves the use of nucleosides comprising any of 5'-O-dimethoxytrityl, 2'-O-tert-butyldimethylsilyl, 3'-O-2-Cyanoethyl N,N-diisopropylphosphoroamidite groups, and exocyclic amine protecting groups (e.g. N6-benzoyl adenosine,

N4 acetyl cytidine, and N2-isobutyryl guanosine). Alternately, 2′-O-Silyl Ethers can be used in conjunction with acid-labile 2′-O-orthoester protecting groups in the synthesis of RNA as described by Scaringe *supra*. Differing 2' chemistries can require different protecting groups, for example 2'-deoxy-2'-amino nucleosides can utilize N-phthaloyl protection as described by Usman *et al.*, US Patent 5,631,360, incorporated by reference herein in its entirety).

During solid phase synthesis, each nucleotide is added sequentially (3′- to 5′-direction) to the solid support-bound oligonucleotide. The first nucleoside at the 3′-end of the chain is covalently attached to a solid support (e.g., controlled pore glass or polystyrene) using various linkers. The nucleotide precursor, a ribonucleoside phosphoramidite, and activator are combined resulting in the coupling of the second nucleoside phosphoramidite onto the 5′-end of the first nucleoside. The support is then washed and any unreacted 5′-hydroxyl groups are capped with a capping reagent such as acetic anhydride to yield inactive 5′-acetyl moieties. The trivalent phosphorus linkage is then oxidized to a more stable phosphate linkage. At the end of the nucleotide addition cycle, the 5′-O-protecting group is cleaved under suitable conditions (e.g., acidic conditions for trityl-based groups and Fluoride for silyl-based groups). The cycle is repeated for each subsequent nucleotide.

Modification of synthesis conditions can be used to optimize coupling efficiency, for example by using differing coupling times, differing reagent/phosphoramidite concentrations, differing contact times, differing solid supports and solid support linker chemistries depending on the particular chemical composition of the siNA to be synthesized. Deprotection and purification of the siNA can be performed as is generally described in Deprotection and purification of the siNA can be performed as is generally described in Usman *et al.*, US 5,831,071, US 6,353,098, US 6,437,117, and Bellon *et al.*, US 6,054,576, US 6,162,909, US 6,303,773, or Scaringe *supra*, incorporated by reference herein in their entireties. Additionally, deprotection conditions can be modified to provide the best possible yield and purity of siNA constructs. For example, applicant has observed that oligonucleotides comprising 2'-deoxy-2'-fluoro nucleotides can degrade under inappropriate deprotection conditions. Such oligonucleotides are deprotected using aqueous methylamine at about 35°C for 30 minutes. If the 2'-deoxy-

2'-fluoro containing oligonucleotide also comprises ribonucleotides, after deprotection with aqueous methylamine at about 35°C for 30 minutes, TEA-HF is added and the reaction maintained at about 65°C for an additional 15 minutes.

Example 6: RNAi *in vitro* assay to assess siNA activity

An *in vitro* assay that recapitulates RNAi in a cell-free system is used to evaluate siNA constructs targeting HD RNA targets. The assay comprises the system described by Tuschl *et al.*, 1999, *Genes and Development*, 13, 3191-3197 and Zamore *et al.*, 2000, *Cell*, 101, 25-33 adapted for use with HD target RNA. A Drosophila extract derived from syncytial blastoderm is used to reconstitute RNAi activity *in vitro*. Target RNA is generated via *in vitro* transcription from an appropriate HD expressing plasmid using T7 RNA polymerase or via chemical synthesis as described herein. Sense and antisense siNA strands (for example 20 uM each) are annealed by incubation in buffer (such as 100 mM potassium acetate, 30 mM HEPES-KOH, pH 7.4, 2 mM magnesium acetate) for 1 minute at 90°C followed by 1 hour at 37°C , then diluted in lysis buffer (for example 100 mM potassium acetate, 30 mM HEPES-KOH at pH 7.4, 2mM magnesium acetate). Annealing can be monitored by gel electrophoresis on an agarose gel in TBE buffer and stained with ethidium bromide. The Drosophila lysate is prepared using zero to two-hour-old embryos from Oregon R flies collected on yeasted molasses agar that are dechorionated and lysed. The lysate is centrifuged and the supernatant isolated. The assay comprises a reaction mixture containing 50% lysate [vol/vol], RNA (10-50 pM final concentration), and 10% [vol/vol] lysis buffer containing siNA (10 nM final concentration). The reaction mixture also contains 10 mM creatine phosphate, 10 ug.ml creatine phosphokinase, 100 um GTP, 100 uM UTP, 100 uM CTP, 500 uM ATP, 5 mM DTT, 0.1 U/uL RNasin (Promega), and 100 uM of each amino acid. The final concentration of potassium acetate is adjusted to 100 mM. The reactions are pre-assembled on ice and preincubated at 25° C for 10 minutes before adding RNA, then incubated at 25° C for an additional 60 minutes. Reactions are quenched with 4 volumes of 1.25 x Passive Lysis Buffer (Promega). Target RNA cleavage is assayed by RT-PCR analysis or other methods known in the art and are compared to control reactions in which siNA is omitted from the reaction.

Alternately, internally-labeled target RNA for the assay is prepared by *in vitro* transcription in the presence of [alpha-^{32}P] CTP, passed over a G 50 Sephadex column by spin chromatography and used as target RNA without further purification. Optionally, target RNA is 5'-^{32}P-end labeled using T4 polynucleotide kinase enzyme. Assays are performed as described above and target RNA and the specific RNA cleavage products generated by RNAi are visualized on an autoradiograph of a gel. The percentage of cleavage is determined by Phosphor Imager® quantitation of bands representing intact control RNA or RNA from control reactions without siNA and the cleavage products generated by the assay.

In one embodiment, this assay is used to determine target sites the HD RNA target for siNA mediated RNAi cleavage, wherein a plurality of siNA constructs are screened for RNAi mediated cleavage of the HD RNA target, for example, by analyzing the assay reaction by electrophoresis of labeled target RNA, or by northern blotting, as well as by other methodology well known in the art.

Example 7: Nucleic acid inhibition of HD target RNA *in vitro*

siNA molecules targeted to the human HD RNA are designed and synthesized as described above. These nucleic acid molecules can be tested for cleavage activity *in vivo*, for example, using the following procedure. The target sequences and the nucleotide location within the HD RNA are given in **Table II and III**.

Two formats are used to test the efficacy of siNAs targeting HD. First, the reagents are tested in cell culture using, for example, COS-1, PC12 or A375 cells to determine the extent of RNA and protein inhibition. siNA reagents (*e.g.*; see **Tables II and III**) are selected against the HD target as described herein. RNA inhibition is measured after delivery of these reagents by a suitable transfection agent to, for example, COS-1, PC12 or A375 cells. Relative amounts of target RNA are measured versus actin using real-time PCR monitoring of amplification (*eg.*, ABI 7700 Taqman®). A comparison is made to a mixture of oligonucleotide sequences made to unrelated targets or to a randomized siNA control with the same overall length and chemistry, but randomly substituted at each position. Primary and secondary lead reagents are chosen

for the target and optimization performed. After an optimal transfection agent concentration is chosen, a RNA time-course of inhibition is performed with the lead siNA molecule. In addition, a cell-plating format can be used to determine RNA inhibition.

Delivery of siNA to Cells

Cells (e.g., COS-1, PC12 or A375 cells) are seeded, for example, at $1x10^5$ cells per well of a six-well dish in EGM-2 (BioWhittaker) the day before transfection. siNA (final concentration, for example 20nM) and cationic lipid (e.g., final concentration 2μg/ml) are complexed in EGM basal media (Biowhittaker) at 37°C for 30 minutes in polystyrene tubes. Following vortexing, the complexed siNA is added to each well and incubated for the times indicated. For initial optimization experiments, cells are seeded, for example, at $1x10^3$ in 96 well plates and siNA complex added as described. Efficiency of delivery of siNA to cells is determined using a fluorescent siNA complexed with lipid. Cells in 6-well dishes are incubated with siNA for 24 hours, rinsed with PBS and fixed in 2% paraformaldehyde for 15 minutes at room temperature. Uptake of siNA is visualized using a fluorescent microscope.

Taqman and Lightcycler quantification of mRNA

Total RNA is prepared from cells following siNA delivery, for example, using Qiagen RNA purification kits for 6-well or Rneasy extraction kits for 96-well assays. For Taqman analysis, dual-labeled probes are synthesized with the reporter dye, FAM or JOE, covalently linked at the 5'-end and the quencher dye TAMRA conjugated to the 3'-end. One-step RT-PCR amplifications are performed on, for example, an ABI PRISM 7700 Sequence Detector using 50 μl reactions consisting of 10 μl total RNA, 100 nM forward primer, 900 nM reverse primer, 100 nM probe, 1X TaqMan PCR reaction buffer (PE-Applied Biosystems), 5.5 mM $MgCl_2$, 300 μM each dATP, dCTP, dGTP, and dTTP, 10U RNase Inhibitor (Promega), 1.25U AmpliTaq Gold (PE-Applied Biosystems) and 10U M-MLV Reverse Transcriptase (Promega). The thermal cycling conditions can consist of 30 minutes at 48°C, 10 minutes at 95°C, followed by 40 cycles of 15 seconds at 95°C and 1 minute at 60°C. Quantitation of mRNA levels is determined relative to standards generated from serially diluted total cellular RNA (300, 100, 33, 11 ng/rxn)

and normalizing to ß-actin or GAPDH mRNA in parallel TaqMan reactions. For each gene of interest an upper and lower primer and a fluorescently labeled probe are designed. Real time incorporation of SYBR Green I dye into a specific PCR product can be measured in glass capillary tubes using a lightcyler. A standard curve is generated for each primer pair using control cRNA. Values are represented as relative expression to GAPDH in each sample.

Western blotting

Nuclear extracts can be prepared using a standard micro preparation technique (see for example Andrews and Faller, 1991, *Nucleic Acids Research,* 19, 2499). Protein extracts from supernatants are prepared, for example using TCA precipitation. An equal volume of 20% TCA is added to the cell supernatant, incubated on ice for 1 hour and pelleted by centrifugation for 5 minutes. Pellets are washed in acetone, dried and resuspended in water. Cellular protein extracts are run on a 10% Bis-Tris NuPage (nuclear extracts) or 4-12% Tris-Glycine (supernatant extracts) polyacrylamide gel and transferred onto nitro-cellulose membranes. Non-specific binding can be blocked by incubation, for example, with 5% non-fat milk for 1 hour followed by primary antibody for 16 hour at 4°C. Following washes, the secondary antibody is applied, for example (1:10,000 dilution) for 1 hour at room temperature and the signal detected with SuperSignal reagent (Pierce).

Other Assays

Other useful assays in evaluating siNA molecules of the invention are described in Davidson *et al.,* WO 04/013280.

Example 8: Animal Models useful to evaluate the down-regulation of HD gene expression

Evaluating the efficacy of anti-HD agents in animal models is an important prerequisite to human clinical trials. Although the HD mRNA and protein product (huntingtin) show widespread distribution, the progressive neurodegeneration is selective in location, with regional neuron loss and gliosis in striatum, cerebral cortex, thalamus, subthalamus, and hippocampus. An experimental transgenic mouse model has utilized

widespread expression of full-length human HD cDNA in mice with either 16, 48, or 89 CAG repeats. Only mice with 48 or 89 CAG repeats manifested progressive behavioral and motor dysfunction with neuron loss and gliosis in striatum, cerebral cortex, thalamus, and hippocampus (Reddy *et al., 1998, Nature Genet.* 20, 198-202). These animals represent a clinically relevant model for HD pathogenesis and can provide insight into the underlying pathophysiologic mechanisms of other triplet repeat disorders. Other neurodegenerative animal models as are known in the art can similarly be utilized to evaluate siNA molecules of the invention, for example models that utilize systemic or localized delivery (e.g., direct injection, intrathecal delivery, osmotic pump etc.) of therapeutic compounds to the CNS, (see for example Ryu *et al.,* 2003, Exp Neurol., 183, 700-4). As such, this model provides an animal model for testing therapeutic drugs, including siNA constructs of the instant invention.

Example 9: RNAi mediated inhibition of HD expression in cell culture

Inhibition of HD RNA expression using siNA targeting HD RNA

siNA constructs (**Table III**) are tested for efficacy in reducing HD RNA expression in, for example, COS-1 cells. Cells are plated approximately 24 hours before transfection in 96-well plates at 5,000-7,500 cells/well, 100 µl/well, such that at the time of transfection cells are 70-90% confluent. For transfection, annealed siNAs are mixed with the transfection reagent (Lipofectamine 2000, Invitrogen) in a volume of 50 µl/well and incubated for 20 min. at room temperature. The siNA transfection mixtures are added to cells to give a final siNA concentration of 25 nM in a volume of 150 µl. Each siNA transfection mixture is added to 3 wells for triplicate siNA treatments. Cells are incubated at 37° for 24h in the continued presence of the siNA transfection mixture. At 24h, RNA is prepared from each well of treated cells. The supernatants with the transfection mixtures are first removed and discarded, then the cells are lysed and RNA prepared from each well. Target gene expression following treatment is evaluated by RT-PCR for the target gene and for a control gene (36B4, an RNA polymerase subunit) for normalization. The triplicate data is averaged and the standard deviations determined for each treatment. Normalized data are graphed and the percent reduction of target mRNA by active siNAs in comparison to their respective inverted control siNAs is determined.

Example 10: Indications

The present body of knowledge in HD research indicates the need for methods to assay HD activity and for compounds that can regulate HD expression for research, diagnostic, and therapeutic use. As described herein, the nucleic acid molecules of the present invention can be used in assays to diagnose disease state related of HD levels. In addition, the nucleic acid molecules can be used to treat disease state related to HD levels.

Particular conditions and disease states that can be associated with HD expression modulation include, but are not limited to Huntinton disease and related conditions such as progressive chorea, rigidity, dementia, and seizures, spinocerebellar ataxia, spinal and bulbar muscular dystrophy (SBMA), dentatorubropallidoluysian atrophy (DRPLA), and any other diseases or conditions that are related to or will respond to the levels of a repeat expansion (RE) protein in a cell or tissue, alone or in combination with other therapies.

The use of caspase inhibitors, agents that disrupt RE protein aggregation, and neuroprotective agents (e.g., pryridoxine) are non-limiting examples of chemotherapeutic agents that can be combined with or used in conjunction with the nucleic acid molecules (*e.g.* siNA molecules) of the instant invention. Those skilled in the art will recognize that other anti-cancer compounds and therapies can similarly be readily combined with the nucleic acid molecules of the instant invention (*e.g.* siNA molecules) and are hence within the scope of the instant invention.

Example 11: Diagnostic uses

The siNA molecules of the invention can be used in a variety of diagnostic applications, such as in the identification of molecular targets (e.g., RNA) in a variety of applications, for example, in clinical, industrial, environmental, agricultural and/or research settings. Such diagnostic use of siNA molecules involves utilizing reconstituted RNAi systems, for example, using cellular lysates or partially purified cellular lysates. siNA molecules of this invention can be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of endogenous or

exogenous, for example viral, RNA in a cell. The close relationship between siNA activity and the structure of the target RNA allows the detection of mutations in any region of the molecule, which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple siNA molecules described in this invention, one can map nucleotide changes, which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with siNA molecules can be used to inhibit gene expression and define the role of specified gene products in the progression of disease or infection. In this manner, other genetic targets can be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple siNA molecules targeted to different genes, siNA molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations siNA molecules and/or other chemical or biological molecules). Other *in vitro* uses of siNA molecules of this invention are well known in the art, and include detection of the presence of mRNAs associated with a disease, infection, or related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a siNA using standard methodologies, for example, fluorescence resonance emission transfer (FRET).

In a specific example, siNA molecules that cleave only wild-type or mutant forms of the target RNA are used for the assay. The first siNA molecules (*i.e.*, those that cleave only wild-type forms of target RNA) are used to identify wild-type RNA present in the sample and the second siNA molecules (*i.e.*, those that cleave only mutant forms of target RNA) are used to identify mutant RNA in the sample. As reaction controls, synthetic substrates of both wild-type and mutant RNA are cleaved by both siNA molecules to demonstrate the relative siNA efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus, each analysis requires two siNA molecules, two substrates and one unknown sample, which is combined into six reactions. The presence of cleavage products is determined using an RNase protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain

insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, disease related or infection related) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels is adequate and decreases the cost of the initial diagnosis. Higher mutant form to wild-type ratios are correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications can be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims. The present invention teaches one skilled in the art to test various combinations and/or substitutions of chemical modifications described herein toward generating nucleic acid constructs with improved activity for mediating RNAi activity. Such improved activity can comprise improved stability, improved bioavailability, and/or improved activation of cellular responses mediating RNAi. Therefore, the specific embodiments described herein are not limiting and one skilled in the art can readily appreciate that specific combinations of the modifications described herein can be tested without undue experimentation toward identifying siNA molecules with improved RNAi activity.

The invention illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Table I: POLYQ repeat Accession Numbers

NM_002111
Homo sapiens huntingtin (Huntington disease) (HD), mRNA
gi|38788404|ref|NM_002111.4|[38788404]

AB016794
Homo sapiens mRNA for huntingtin, complete cds
gi|4126798|dbj|AB016794.1|[4126798]

L12392
Homo sapiens Huntington's Disease (HD) mRNA, complete cds
gi|1709991|gb|L12392.1|HUMHDA[1709991]

AC005516
Homo sapiens Chromosome 4p16.3 BAC clone 399e10 containing Huntington's Disease
gene; exons 1-67, complete sequence
gi|3900835|gb|AC005516.1|AC005516[3900835]

AL390059
Human DNA sequence from clone RP11-399E10 on chromosome 4, complete sequence
gi|26984367|emb|AL390059.9|[26984367]

Z69837
Human DNA sequence from clone LA04NC01-113B6 on chromosome 4, complete sequence
gi|1212949|emb|Z69837.1|HSL113B6[1212949]

L20431
Homo sapiens Huntington disease-associated protein (HD) mRNA, complete cds
gi|398028|gb|L20431.1|HUMHUNTDIS[398028]

NM_000332
Homo sapiens spinocerebellar ataxia 1 (olivopontocerebellar ataxia 1, autosomal
dominant, ataxin 1) (SCA1), mRNA
gi|4506792|ref|NM_000332.1|[4506792]

X79204
H.sapiens SCA1 mRNA for ataxin
gi|529661|emb|X79204.1|HSSCA1[529661]

AL009031
Human DNA sequence from clone RP3-467D16 on chromosome 6p22.3-24.1 Contains the
5' end of the SCA1 gene for spinocerebellar ataxia 1 (olivopontocerebellar
ataxia 1, autosomal dominant, ataxin 1) with a poly-glutamine (CAG repeat)
polymorphism and the 3' part of the GMPR gene for GMP reductase, Guanosine
5'-monophosphate oxidoreductase, complete sequence
gi|2808422|emb|AL009031.1|HS467D16[2808422]

S64648
SCA1 {CAG repeat} [human, Genomic Mutant, 506 nt]
gi|407593|bbm|316393|bbs|136468|gb|S64648.1|S64648[407593]

BC047894
Homo sapiens spinocerebellar ataxia 1 (olivopontocerebellar ataxia 1, autosomal
dominant, ataxin 1), mRNA (cDNA clone IMAGE:4472404), partial cds
gi|28839052|gb|BC047894.1|[28839052]

NM_002973
Homo sapiens spinocerebellar ataxia 2 (olivopontocerebellar ataxia 2, autosomal
dominant, ataxin 2) (SCA2), mRNA
gi|4506794|ref|NM_002973.1|[4506794]

U70323
Human ataxin-2 (SCA2) mRNA, complete cds
gi|1679683|gb|U70323.1|HSU70323[1679683]

Y08262
H.sapiens mRNA for SCA2 protein
gi|1770389|emb|Y08262.1|HSDANSCA2[1770389]

AK095017
Homo sapiens cDNA FLJ37698 fis, clone BRHIP2015679, highly similar to Human
ataxin-2 (SCA2) mRNA
gi|21754198|dbj|AK095017.1|[21754198]

BC033711
Homo sapiens Machado-Joseph disease (spinocerebellar ataxia 3,
olivopontocerebellar ataxia 3, autosomal dominant, ataxin 3), mRNA (cDNA clone
MGC:44934 IMAGE:4393766), complete cds
gi|21708051|gb|BC033711.1|[21708051]

U64822
Homo sapiens josephin MJD1 mRNA, partial cds
gi|2262198|gb|U64822.1|HSU64822[2262198]

S75313
MJD1=MJD1 protein {CAG repeats} [human, brain, mRNA, 1776 nt]
gi|833927|bbm|360325|bbs|160590|gb|S75313.1|S75313[833927]

NM_004993
Homo sapiens Machado-Joseph disease (spinocerebellar ataxia 3,
olivopontocerebellar ataxia 3, autosomal dominant, ataxin 3) (MJD), transcript
variant 1, mRNA
gi|13518018|ref|NM_004993.2|[13518018]

U64821
Homo sapiens josephin MJD1 mRNA, cds
gi|2262196|gb|U64821.1|HSU64821[2262196]

U64820
Homo sapiens josephin MJD1 mRNA, complete cds
gi|2262194|gb|U64820.1|HSU64820[2262194]

AB050194
Homo sapiens mRNA for ataxin-3, complete cds

gi|11559485|dbj|AB050194.1|[11559485]

NM_030660
Homo sapiens Machado-Joseph disease (spinocerebellar ataxia 3,
olivopontocerebellar ataxia 3, autosomal dominant, ataxin 3) (MJD), transcript
variant 2, mRNA
gi|13518012|ref|NM_030660.1|[13518012]

BC022245
Homo sapiens Machado-Joseph disease (spinocerebellar ataxia 3,
olivopontocerebellar ataxia 3, autosomal dominant, ataxin 3), mRNA (cDNA clone
IMAGE:4717161), containing frame-shift errors
gi|18490814|gb|BC022245.1|[18490814]

AB038653
Homo sapiens genomic DNA, chromosome 14q32.1, BAC clone:B445M7
gi|14149091|dbj|AB038653.1|[14149091]

AJ000501
Homo sapiens DNA for CAG/CTG repeat region
gi|2274960|emb|AJ000501.1|HSCAGCTG[2274960]

NM_000068
Homo sapiens calcium channel, voltage-dependent, P/Q type, alpha 1A subunit
(CACNA1A), transcript variant 1, mRNA
gi|13386499|ref|NM_000068.2|[13386499]

NM_023035
Homo sapiens calcium channel, voltage-dependent, P/Q type, alpha 1A subunit
(CACNA1A), transcript variant 2, mRNA
gi|13386497|ref|NM_023035.1|[13386497]

U79666
Homo sapiens alpha1A-voltage-dependent calcium channel mRNA, splice form

BI-1-Vi-GGCAG, complete cds
gi|2281751|gb|U79666.1|HSU79666[2281751]

X99897
H.sapiens mRNA for P/Q-type calcium channel alpha1 subunit
gi|1657332|emb|X99897.1|HSPQCCA1[1657332]

AB035726
Homo sapiens CACNA1A mRNA for alpha1A-voltage-dependent calcium channel, partial
cds, isolate:TMDN-SCA6-001
gi|7630180|dbj|AB035726.1|[7630180]

AF004883
Homo sapiens neuronal calcium channel alpha 1A subunit isoform 1A-2 mRNA,
complete cds
gi|2213910|gb|AF004883.1|AF004883[2213910]

AF004884
Homo sapiens neuronal calcium channel alpha 1A subunit isoform A-1 mRNA,
complete cds
gi|2213912|gb|AF004884.1|AF004884[2213912]

AB035727
Homo sapiens CACNA1A mRNA for alpha1A-voltage-dependent calcium channel,
complete cds, isolate:TMDN-CNT-001
gi|9711928|dbj|AB035727.2|[9711928]

U06702
Human clone CCA54 mRNA containing CCA trinucleotide repeat
gi|476266|gb|U06702.1|HSU06702[476266]

NM_000333
Homo sapiens spinocerebellar ataxia 7 (olivopontocerebellar atrophy with retinal
degeneration) (SCA7), mRNA
gi|4506796|ref|NM_000333.1|[4506796]

AJ000517
Homo Sapiens mRNA for spinocerebellar ataxia 7
gi|2370154|emb|AJ000517.1|HSSCA7[2370154]

AF032105
Homo sapiens ataxin-7 (SCA7) mRNA, complete cds
gi|3192953|gb|AF032105.1|AF032105[3192953]

AF032103
Homo sapiens ataxin-7 (SCA7) mRNA, 3' end, partial cds
gi|3192949|gb|AF032103.1|AF032103[3192949]

AK125125
Homo sapiens cDNA FLJ43135 fis, clone CTONG3006629
gi|34531113|dbj|AK125125.1|[34531113]

AF020275
Homo sapiens expanded SCA7 CAG repeat
gi|2501955|gb|AF020275.1|AF020275[2501955]

NM_004576
Homo sapiens protein phosphatase 2 (formerly 2A),
regulatory subunit B (PR 52),
beta isoform (PPP2R2B), transcript variant 1, mRNA
gi|32307122|ref|NM_004576.2|[32307122]

M64930
Human protein phosphatase 2A beta subunit mRNA, complete
cds
gi|190423|gb|M64930.1|HUMPROP2AB[190423]

NM_181675
Homo sapiens protein phosphatase 2 (formerly 2A),
regulatory subunit B (PR 52),
beta isoform (PPP2R2B), transcript variant 3, mRNA
gi|32307114|ref|NM_181675.1|[32307114]

NM_181674
Homo sapiens protein phosphatase 2 (formerly 2A),
regulatory subunit B (PR 52),
beta isoform (PPP2R2B), transcript variant 2, mRNA

gi|32307112|ref|NM_181674.1|[32307112]

BC031790
Homo sapiens protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), beta isoform, transcript variant 2, mRNA (cDNA clone MGC:24888 IMAGE:4939981), complete cds
gi|21619304|gb|BC031790.1|[21619304]

AK056192
Homo sapiens cDNA FLJ31630 fis, clone NT2RI2003361, highly similar to PROTEIN PHOSPHATASE PP2A, 55 KD REGULATORY SUBUNIT, NEURONAL ISOFORM
gi|16551529|dbj|AK056192.1|[16551529]

NM_000044
Homo sapiens androgen receptor (dihydrotestosterone receptor; testicular feminization; spinal and bulbar muscular atrophy; Kennedy disease) (AR), mRNA
gi|21322251|ref|NM_000044.2|[21322251]

M20132
Human androgen receptor (AR) mRNA, complete cds
gi|178627|gb|M20132.1|HUMANDREC[178627]

M21748
Human androgen receptor mRNA, complete cds, clones A1 and J8
gi|178871|gb|M21748.1|HUMARA[178871]

M73069
Human androgen receptor mutant gene, mRNA, complete cds
gi|178655|gb|M73069.1|HUMANRE[178655]

BC051795
Homo sapiens dentatorubral-pallidoluysian atrophy (atrophin-1), mRNA (cDNA clone MGC:57647 IMAGE:4181592), complete cds
gi|34193087|gb|BC051795.2|[34193087]

NM_001940
Homo sapiens dentatorubral-pallidoluysian atrophy
(atrophin-1) (DRPLA), mRNA
gi|6005998|ref|NM_001940.2|[6005998]

U23851
Human atrophin-1 mRNA, complete cds
gi|915325|gb|U23851.1|HSU23851[915325]

D38529
Homo sapiens mRNA for DRPLA protein, complete cds
gi|1732443|dbj|D38529.1|HUMDRPLA[1732443]

D31840
Homo sapiens DRPLA mRNA, complete cds
gi|862329|dbj|D31840.1|HUMDRPLA1[862329]

AC006512
Homo sapiens 12 PAC RP3-461F17 (Roswell Park Cancer
Institute Human PAC Library)
complete sequence
gi|29469488|gb|AC006512.13|[29469488]

Table II: HD siNA and Target Sequences

dbSNP ID	Pos	Target Seq	Seq ID	UPos	Upper seq	SeqID	LPos	Lower seq	Seq ID
rs396875	85	CAAUCAUGCUGGCCGGCGU	1	85	CAAUCAUGCUGGCCGGCGU	1	103	ACGCCGGCCAGCAUGAUUG	1753
rs396875	86	AAUCAUGCUGGCCGGCGUG	2	86	AAUCAUGCUGGCCGGCGUG	2	104	CACGCCGGCCAGCAUGAUU	1754
rs396875	87	AUCAUGCUGGCCGGCGUGG	3	87	AUCAUGCUGGCCGGCGUGG	3	105	CCACGCCGGCCAGCAUGAU	1755
rs396875	88	UCAUGCUGGCCGGCGUGGC	4	88	UCAUGCUGGCCGGCGUGGC	4	106	GCCACGCCGGCCAGCAUGA	1756
rs396875	89	CAUGCUGGCCGGCGUGGCC	5	89	CAUGCUGGCCGGCGUGGCC	5	107	GGCCACGCCGGCCAGCAUG	1757
rs396875	90	AUGCUGGCCGGCGUGGCCC	6	90	AUGCUGGCCGGCGUGGCCC	6	108	GGGCCACGCCGGCCAGCAU	1758
rs396875	91	UGCUGGCCGGCGUGGCCCC	7	91	UGCUGGCCGGCGUGGCCCC	7	109	GGGGCCACGCCGGCCAGCA	1759
rs396875	92	GCUGGCCGGCGUGGCCCCG	8	92	GCUGGCCGGCGUGGCCCCG	8	110	CGGGGCCACGCCGGCCAGC	1760
rs396875	93	CUGGCCGGCGUGGCCCCGC	9	93	CUGGCCGGCGUGGCCCCGC	9	111	GCGGGGCCACGCCGGCCAG	1761
rs396875	94	UGGCCGGCGUGGCCCCGCC	10	94	UGGCCGGCGUGGCCCCGCC	10	112	GGCGGGGCCACGCCGGCCA	1762
rs396875	95	GGCCGGCGUGGCCCCGCCU	11	95	GGCCGGCGUGGCCCCGCCU	11	113	AGGCGGGGCCACGCCGGCC	1763
rs396875	96	GCCGGCGUGGCCCCGCCUC	12	96	GCCGGCGUGGCCCCGCCUC	12	114	GAGGCGGGGCCACGCCGGC	1764
rs396875	97	CCGGCGUGGCCCCGCCUCC	13	97	CCGGCGUGGCCCCGCCUCC	13	115	GGAGGCGGGGCCACGCCGG	1765
rs396875	98	CGGCGUGGCCCCGCCUCCG	14	98	CGGCGUGGCCCCGCCUCCG	14	116	CGGAGGCGGGGCCACGCCG	1766
rs396875	99	GGCGUGGCCCCGCCUCCGC	15	99	GGCGUGGCCCCGCCUCCGC	15	117	GCGGAGGCGGGGCCACGCC	1767
rs396875	100	GCGUGGCCCCGCCUCCGCC	16	100	GCGUGGCCCCGCCUCCGCC	16	118	GGCGGAGGCGGGGCCACGC	1768
rs396875	101	CGUGGCCCCGCCUCCGCCG	17	101	CGUGGCCCCGCCUCCGCCG	17	119	CGGCGGAGGCGGGGCCACG	1769
rs396875	102	GUGGCCCCGCCUCCGCCGG	18	102	GUGGCCCCGCCUCCGCCGG	18	120	CCGGCGGAGGCGGGGCCAC	1770
rs396875	103	UGGCCCCGCCUCCGCCGGC	19	103	UGGCCCCGCCUCCGCCGGC	19	121	GCCGGCGGAGGCGGGGCCA	1771
rs396875	85	CAAUCAUGCUGGCCGGCGC	20	85	CAAUCAUGCUGGCCGGCGC	20	103	GCGCCGGCCAGCAUGAUUG	1772
rs396875	86	AAUCAUGCUGGCCGGCGCG	21	86	AAUCAUGCUGGCCGGCGCG	21	104	CGCGCCGGCCAGCAUGAUU	1773
rs396875	87	AUCAUGCUGGCCGGCGCGG	22	87	AUCAUGCUGGCCGGCGCGG	22	105	CCGCGCCGGCCAGCAUGAU	1774
rs396875	88	UCAUGCUGGCCGGCGCGGC	23	88	UCAUGCUGGCCGGCGCGGC	23	106	GCCGCGCCGGCCAGCAUGA	1775
rs396875	89	CAUGCUGGCCGGCGCGGCC	24	89	CAUGCUGGCCGGCGCGGCC	24	107	GGCCGCGCCGGCCAGCAUG	1776
rs396875	90	AUGCUGGCCGGCGCGGCCC	25	90	AUGCUGGCCGGCGCGGCCC	25	108	GGGCCGCGCCGGCCAGCAU	1777
rs396875	91	UGCUGGCCGGCGCGGCCCC	26	91	UGCUGGCCGGCGCGGCCCC	26	109	GGGGCCGCGCCGGCCAGCA	1778
rs396875	92	GCUGGCCGGCGCGGCCCCG	27	92	GCUGGCCGGCGCGGCCCCG	27	110	CGGGGCCGCGCCGGCCAGC	1779
rs396875	93	CUGGCCGGCGCGGCCCCGC	28	93	CUGGCCGGCGCGGCCCCGC	28	111	GCGGGGCCGCGCCGGCCAG	1780
rs396875	94	UGGCCGGCGCGGCCCCGCC	29	94	UGGCCGGCGCGGCCCCGCC	29	112	GGCGGGGCCGCGCCGGCCA	1781
rs396875	95	GGCCGGCGCGGCCCCGCCU	30	95	GGCCGGCGCGGCCCCGCCU	30	113	AGGCGGGGCCGCGCCGGCC	1782
rs396875	96	GCCGGCGCGGCCCCGCCUC	31	96	GCCGGCGCGGCCCCGCCUC	31	114	GAGGCGGGGCCGCGCCGGC	1783
rs396875	97	CCGGCGCGGCCCCGCCUCC	32	97	CCGGCGCGGCCCCGCCUCC	32	115	GGAGGCGGGGCCGCGCCGG	1784
rs396875	98	CGGCGCGGCCCCGCCUCCG	33	98	CGGCGCGGCCCCGCCUCCG	33	116	CGGAGGCGGGGCCGCGCCG	1785
rs396875	99	GGCGCGGCCCCGCCUCCGC	34	99	GGCGCGGCCCCGCCUCCGC	34	117	GCGGAGGCGGGGCCGCGCC	1786
rs396875	100	GCGCGGCCCCGCCUCCGCC	35	100	GCGCGGCCCCGCCUCCGCC	35	118	GGCGGAGGCGGGGCCGCGC	1787

rs396875	101	CGCGGCCCCGCCUCCGCCG	36	101	CGCGGCCCCGCCUCCGCCG	36	119	CGGCGGAGGCGGGGCCGCG	1788
rs396875	102	GCGGCCCCGCCUCCGCCGG	37	102	GCGGCCCCGCCUCCGCCGG	37	120	CCGGCGGAGGCGGGGCCGC	1789
rs396875	103	CGGCCCCGCCUCCGCCGGC	38	103	CGGCCCCGCCUCCGCCGGC	38	121	GCCGGCGGAGGCGGGGCCG	1790
rs10701858	328	GAAAAGCUGAUGAAGGCCU	39	328	GAAAAGCUGAUGAAGGCCU	39	346	AGGCCUUCAUCAGCUUUUC	1791
rs10701858	329	AAAAGCUGAUGAAGGCCUU	40	329	AAAAGCUGAUGAAGGCCUU	40	347	AAGGCCUUCAUCAGCUUUU	1792
rs10701858	330	AAAGCUGAUGAAGGCCUUC	41	330	AAAGCUGAUGAAGGCCUUC	41	348	GAAGGCCUUCAUCAGCUUU	1793
rs10701858	331	AAGCUGAUGAAGGCCUUCG	42	331	AAGCUGAUGAAGGCCUUCG	42	349	CGAAGGCCUUCAUCAGCUU	1794
rs10701858	332	AGCUGAUGAAGGCCUUCGA	43	332	AGCUGAUGAAGGCCUUCGA	43	350	UCGAAGGCCUUCAUCAGCU	1795
rs10701858	333	GCUGAUGAAGGCCUUCGAG	44	333	GCUGAUGAAGGCCUUCGAG	44	351	CUCGAAGGCCUUCAUCAGC	1796
rs10701858	334	CUGAUGAAGGCCUUCGAGU	45	334	CUGAUGAAGGCCUUCGAGU	45	352	ACUCGAAGGCCUUCAUCAG	1797
rs10701858	335	UGAUGAAGGCCUUCGAGUC	46	335	UGAUGAAGGCCUUCGAGUC	46	353	GACUCGAAGGCCUUCAUCA	1798
rs10701858	336	GAUGAAGGCCUUCGAGUCC	47	336	GAUGAAGGCCUUCGAGUCC	47	354	GGACUCGAAGGCCUUCAUC	1799
rs10701858	337	AUGAAGGCCUUCGAGUCCC	48	337	AUGAAGGCCUUCGAGUCCC	48	355	GGGACUCGAAGGCCUUCAU	1800
rs10701858	338	UGAAGGCCUUCGAGUCCCU	49	338	UGAAGGCCUUCGAGUCCCU	49	356	AGGGACUCGAAGGCCUUCA	1801
rs10701858	339	GAAGGCCUUCGAGUCCCUC	50	339	GAAGGCCUUCGAGUCCCUC	50	357	GAGGGACUCGAAGGCCUUC	1802
rs10701858	340	AAGGCCUUCGAGUCCCUCA	51	340	AAGGCCUUCGAGUCCCUCA	51	358	UGAGGGACUCGAAGGCCUU	1803
rs10701858	341	AGGCCUUCGAGUCCCUCAA	52	341	AGGCCUUCGAGUCCCUCAA	52	359	UUGAGGGACUCGAAGGCCU	1804
rs10701858	342	GGCCUUCGAGUCCCUCAAG	53	342	GGCCUUCGAGUCCCUCAAG	53	360	CUUGAGGGACUCGAAGGCC	1805
rs10701858	343	GCCUUCGAGUCCCUCAAGU	54	343	GCCUUCGAGUCCCUCAAGU	54	361	ACUUGAGGGACUCGAAGGC	1806
rs10701858	344	CCUUCGAGUCCCUCAAGU	55	344	CCUUCGAGUCCCUCAAGU	55	362	ACUUGAGGGACUCGAAGG	1807
rs10701858	328	GAAAAGCUGAUGAAGGCCG	56	328	GAAAAGCUGAUGAAGGCCG	56	346	CGGCCUUCAUCAGCUUUUC	1808
rs10701858	329	AAAAGCUGAUGAAGGCCGC	57	329	AAAAGCUGAUGAAGGCCGC	57	347	GCGGCCUUCAUCAGCUUUU	1809
rs10701858	330	AAAGCUGAUGAAGGCCGCC	58	330	AAAGCUGAUGAAGGCCGCC	58	348	GGCGGCCUUCAUCAGCUUU	1810
rs10701858	331	AAGCUGAUGAAGGCCGCCU	59	331	AAGCUGAUGAAGGCCGCCU	59	349	AGGCGGCCUUCAUCAGCUU	1811
rs10701858	332	AGCUGAUGAAGGCCGCCUU	60	332	AGCUGAUGAAGGCCGCCUU	60	350	AAGGCGGCCUUCAUCAGCU	1812
rs10701858	333	GCUGAUGAAGGCCGCCUUC	61	333	GCUGAUGAAGGCCGCCUUC	61	351	GAAGGCGGCCUUCAUCAGC	1813
rs10701858	334	CUGAUGAAGGCCGCCUUCG	62	334	CUGAUGAAGGCCGCCUUCG	62	352	CGAAGGCGGCCUUCAUCAG	1814
rs10701858	335	UGAUGAAGGCCGCCUUCGA	63	335	UGAUGAAGGCCGCCUUCGA	63	353	UCGAAGGCGGCCUUCAUCA	1815
rs10701858	336	GAUGAAGGCCGCCUUCGAG	64	336	GAUGAAGGCCGCCUUCGAG	64	354	CUCGAAGGCGGCCUUCAUC	1816
rs10701858	337	AUGAAGGCCGCCUUCGAGU	65	337	AUGAAGGCCGCCUUCGAGU	65	355	ACUCGAAGGCGGCCUUCAU	1817
rs10701858	338	UGAAGGCCGCCUUCGAGUC	66	338	UGAAGGCCGCCUUCGAGUC	66	356	GACUCGAAGGCGGCCUUCA	1818
rs10701858	339	GAAGGCCGCCUUCGAGUCC	67	339	GAAGGCCGCCUUCGAGUCC	67	357	GGACUCGAAGGCGGCCUUC	1819
rs10701858	340	AAGGCCGCCUUCGAGUCCC	68	340	AAGGCCGCCUUCGAGUCCC	68	358	GGGACUCGAAGGCGGCCUU	1820
rs10701858	341	AGGCCGCCUUCGAGUCCCU	69	341	AGGCCGCCUUCGAGUCCCU	69	359	AGGGACUCGAAGGCGGCCU	1821
rs10701858	342	GGCCGCCUUCGAGUCCCUC	70	342	GGCCGCCUUCGAGUCCCUC	70	360	GAGGGACUCGAAGGCGGCC	1822
rs10701858	343	GCCGCCUUCGAGUCCCUCA	71	343	GCCGCCUUCGAGUCCCUCA	71	361	UGAGGGACUCGAAGGCGGC	1823
rs10701858	344	CCGCCUUCGAGUCCCUCAA	72	344	CCGCCUUCGAGUCCCUCAA	72	362	UUGAGGGACUCGAAGGCGG	1824
rs10701858	345	CGCCUUCGAGUCCCUCAAG	73	345	CGCCUUCGAGUCCCUCAAG	73	363	CUUGAGGGACUCGAAGGCG	1825
rs1936033	1070	UUUUGUUAAAGGCCUUCAU	74	1070	UUUUGUUAAAGGCCUUCAU	74	1088	AUGAAGGCCUUUAACAAAA	1826

rs1936033	1071	UUUGUUAAAGGCCUUCAUA	75	1071	UUUGUUAAAGGCCUUCAUA	75	1089	UAUGAAGGCCUUUAACAAA	1827
rs1936033	1072	UUGUUAAAGGCCUUCAUAG	76	1072	UUGUUAAAGGCCUUCAUAG	76	1090	CUAUGAAGGCCUUUAACAA	1828
rs1936033	1073	UGUUAAAGGCCUUCAUAGC	77	1073	UGUUAAAGGCCUUCAUAGC	77	1091	GCUAUGAAGGCCUUUAACA	1829
rs1936033	1074	GUUAAAGGCCUUCAUAGCG	78	1074	GUUAAAGGCCUUCAUAGCG	78	1092	CGCUAUGAAGGCCUUUAAC	1830
rs1936033	1075	UUAAAGGCCUUCAUAGCGA	79	1075	UUAAAGGCCUUCAUAGCGA	79	1093	UCGCUAUGAAGGCCUUUAA	1831
rs1936033	1076	UAAAGGCCUUCAUAGCGAA	80	1076	UAAAGGCCUUCAUAGCGAA	80	1094	UUCGCUAUGAAGGCCUUUA	1832
rs1936033	1077	AAAGGCCUUCAUAGCGAAC	81	1077	AAAGGCCUUCAUAGCGAAC	81	1095	GUUCGCUAUGAAGGCCUUU	1833
rs1936033	1078	AAGGCCUUCAUAGCGAACC	82	1078	AAGGCCUUCAUAGCGAACC	82	1096	GGUUCGCUAUGAAGGCCUU	1834
rs1936033	1079	AGGCCUUCAUAGCGAACCU	83	1079	AGGCCUUCAUAGCGAACCU	83	1097	AGGUUCGCUAUGAAGGCCU	1835
rs1936033	1080	GGCCUUCAUAGCGAACCUG	84	1080	GGCCUUCAUAGCGAACCUG	84	1098	CAGGUUCGCUAUGAAGGCC	1836
rs1936033	1081	GCCUUCAUAGCGAACCUGA	85	1081	GCCUUCAUAGCGAACCUGA	85	1099	UCAGGUUCGCUAUGAAGGC	1837
rs1936033	1082	CCUUCAUAGCGAACCUGAA	86	1082	CCUUCAUAGCGAACCUGAA	86	1100	UUCAGGUUCGCUAUGAAGG	1838
rs1936033	1083	CUUCAUAGCGAACCUGAAG	87	1083	CUUCAUAGCGAACCUGAAG	87	1101	CUUCAGGUUCGCUAUGAAG	1839
rs1936033	1084	UUCAUAGCGAACCUGAAGU	88	1084	UUCAUAGCGAACCUGAAGU	88	1102	ACUUCAGGUUCGCUAUGAA	1840
rs1936033	1085	UCAUAGCGAACCUGAAGUC	89	1085	UCAUAGCGAACCUGAAGUC	89	1103	GACUUCAGGUUCGCUAUGA	1841
rs1936033	1086	CAUAGCGAACCUGAAGUCA	90	1086	CAUAGCGAACCUGAAGUCA	90	1104	UGACUUCAGGUUCGCUAUG	1842
rs1936033	1087	AUAGCGAACCUGAAGUCAA	91	1087	AUAGCGAACCUGAAGUCAA	91	1105	UUGACUUCAGGUUCGCUAU	1843
rs1936033	1088	UAGCGAACCUGAAGUCAAG	92	1088	UAGCGAACCUGAAGUCAAG	92	1106	CUUGACUUCAGGUUCGCUA	1844
rs1936033	1070	UUUUGUUAAAGGCCUUCAC	93	1070	UUUUGUUAAAGGCCUUCAC	93	1088	GUGAAGGCCUUUAACAAAA	1845
rs1936033	1071	UUUGUUAAAGGCCUUCACA	94	1071	UUUGUUAAAGGCCUUCACA	94	1089	UGUGAAGGCCUUUAACAAA	1846
rs1936033	1072	UUGUUAAAGGCCUUCACAG	95	1072	UUGUUAAAGGCCUUCACAG	95	1090	CUGUGAAGGCCUUUAACAA	1847
rs1936033	1073	UGUUAAAGGCCUUCACAGC	96	1073	UGUUAAAGGCCUUCACAGC	96	1091	GCUGUGAAGGCCUUUAACA	1848
rs1936033	1074	GUUAAAGGCCUUCACAGCG	97	1074	GUUAAAGGCCUUCACAGCG	97	1092	CGCUGUGAAGGCCUUUAAC	1849
rs1936033	1075	UUAAAGGCCUUCACAGCGA	98	1075	UUAAAGGCCUUCACAGCGA	98	1093	UCGCUGUGAAGGCCUUUAA	1850
rs1936033	1076	UAAAGGCCUUCACAGCGAA	99	1076	UAAAGGCCUUCACAGCGAA	99	1094	UUCGCUGUGAAGGCCUUUA	1851
rs1936033	1077	AAAGGCCUUCACAGCGAAC	100	1077	AAAGGCCUUCACAGCGAAC	100	1095	GUUCGCUGUGAAGGCCUUU	1852
rs1936033	1078	AAGGCCUUCACAGCGAACC	101	1078	AAGGCCUUCACAGCGAACC	101	1096	GGUUCGCUGUGAAGGCCUU	1853
rs1936033	1079	AGGCCUUCACAGCGAACCU	102	1079	AGGCCUUCACAGCGAACCU	102	1097	AGGUUCGCUGUGAAGGCCU	1854
rs1936033	1080	GGCCUUCACAGCGAACCUG	103	1080	GGCCUUCACAGCGAACCUG	103	1098	CAGGUUCGCUGUGAAGGCC	1855
rs1936033	1081	GCCUUCACAGCGAACCUGA	104	1081	GCCUUCACAGCGAACCUGA	104	1099	UCAGGUUCGCUGUGAAGGC	1856
rs1936033	1082	CCUUCACAGCGAACCUGAA	105	1082	CCUUCACAGCGAACCUGAA	105	1100	UUCAGGUUCGCUGUGAAGG	1857
rs1936033	1083	CUUCACAGCGAACCUGAAG	106	1083	CUUCACAGCGAACCUGAAG	106	1101	CUUCAGGUUCGCUGUGAAG	1858
rs1936033	1084	UUCACAGCGAACCUGAAGU	107	1084	UUCACAGCGAACCUGAAGU	107	1102	ACUUCAGGUUCGCUGUGAA	1859
rs1936033	1085	UCACAGCGAACCUGAAGUC	108	1085	UCACAGCGAACCUGAAGUC	108	1103	GACUUCAGGUUCGCUGUGA	1860
rs1936033	1086	CACAGCGAACCUGAAGUCA	109	1086	CACAGCGAACCUGAAGUCA	109	1104	UGACUUCAGGUUCGCUGUG	1861
rs1936033	1087	ACAGCGAACCUGAAGUCAA	110	1087	ACAGCGAACCUGAAGUCAA	110	1105	UUGACUUCAGGUUCGCUGU	1862
rs1936033	1088	CAGCGAACCUGAAGUCAAG	111	1088	CAGCGAACCUGAAGUCAAG	111	1106	CUUGACUUCAGGUUCGCUG	1863
rs1936032	1188	UUGGCUACUAAAUGUGCUC	112	1188	UUGGCUACUAAAUGUGCUC	112	1206	GAGCACAUUUAGUAGCCAA	1864
rs1936032	1189	UGGCUACUAAAUGUGCUCU	113	1189	UGGCUACUAAAUGUGCUCU	113	1207	AGAGCACAUUUAGUAGCCA	1865

rs1936032	1190	GGCUACUAAAUGUGCUCUU	114	1190	GGCUACUAAAUGUGCUCUU	114	1208	AAGAGCACAUUUAGUAGCC	1866
rs1936032	1191	GCUACUAAAUGUGCUCUUA	115	1191	GCUACUAAAUGUGCUCUUA	115	1209	UAAGAGCACAUUUAGUAGC	1867
rs1936032	1192	CUACUAAAUGUGCUCUUAG	116	1192	CUACUAAAUGUGCUCUUAG	116	1210	CUAAGAGCACAUUUAGUAG	1868
rs1936032	1193	UACUAAAUGUGCUCUUAGG	117	1193	UACUAAAUGUGCUCUUAGG	117	1211	CCUAAGAGCACAUUUAGUA	1869
rs1936032	1194	ACUAAAUGUGCUCUUAGGC	118	1194	ACUAAAUGUGCUCUUAGGC	118	1212	GCCUAAGAGCACAUUUAGU	1870
rs1936032	1195	CUAAAUGUGCUCUUAGGCU	119	1195	CUAAAUGUGCUCUUAGGCU	119	1213	AGCCUAAGAGCACAUUUAG	1871
rs1936032	1196	UAAAUGUGCUCUUAGGCUU	120	1196	UAAAUGUGCUCUUAGGCUU	120	1214	AAGCCUAAGAGCACAUUUA	1872
rs1936032	1197	AAAUGUGCUCUUAGGCUUA	121	1197	AAAUGUGCUCUUAGGCUUA	121	1215	UAAGCCUAAGAGCACAUUU	1873
rs1936032	1198	AAUGUGCUCUUAGGCUUAC	122	1198	AAUGUGCUCUUAGGCUUAC	122	1216	GUAAGCCUAAGAGCACAUU	1874
rs1936032	1199	AUGUGCUCUUAGGCUUACU	123	1199	AUGUGCUCUUAGGCUUACU	123	1217	AGUAAGCCUAAGAGCACAU	1875
rs1936032	1200	UGUGCUCUUAGGCUUACUC	124	1200	UGUGCUCUUAGGCUUACUC	124	1218	GAGUAAGCCUAAGAGCACA	1876
rs1936032	1201	GUGCUCUUAGGCUUACUCG	125	1201	GUGCUCUUAGGCUUACUCG	125	1219	CGAGUAAGCCUAAGAGCAC	1877
rs1936032	1202	UGCUCUUAGGCUUACUCGU	126	1202	UGCUCUUAGGCUUACUCGU	126	1220	ACGAGUAAGCCUAAGAGCA	1878
rs1936032	1203	GCUCUUAGGCUUACUCGUU	127	1203	GCUCUUAGGCUUACUCGUU	127	1221	AACGAGUAAGCCUAAGAGC	1879
rs1936032	1204	CUCUUAGGCUUACUCGUUC	128	1204	CUCUUAGGCUUACUCGUUC	128	1222	GAACGAGUAAGCCUAAGAG	1880
rs1936032	1205	UCUUAGGCUUACUCGUUCC	129	1205	UCUUAGGCUUACUCGUUCC	129	1223	GGAACGAGUAAGCCUAAGA	1881
rs1936032	1206	CUUAGGCUUACUCGUUCCU	130	1206	CUUAGGCUUACUCGUUCCU	130	1224	AGGAACGAGUAAGCCUAAG	1882
rs1936032	1188	UUGGCUACUAAAUGUGCUG	131	1188	UUGGCUACUAAAUGUGCUG	131	1206	CAGCACAUUUAGUAGCCAA	1883
rs1936032	1189	UGGCUACUAAAUGUGCUGU	132	1189	UGGCUACUAAAUGUGCUGU	132	1207	ACAGCACAUUUAGUAGCCA	1884
rs1936032	1190	GGCUACUAAAUGUGCUGUU	133	1190	GGCUACUAAAUGUGCUGUU	133	1208	AACAGCACAUUUAGUAGCC	1885
rs1936032	1191	GCUACUAAAUGUGCUGUUA	134	1191	GCUACUAAAUGUGCUGUUA	134	1209	UAACAGCACAUUUAGUAGC	1886
rs1936032	1192	CUACUAAAUGUGCUGUUAG	135	1192	CUACUAAAUGUGCUGUUAG	135	1210	CUAACAGCACAUUUAGUAG	1887
rs1936032	1193	UACUAAAUGUGCUGUUAGG	136	1193	UACUAAAUGUGCUGUUAGG	136	1211	CCUAACAGCACAUUUAGUA	1888
rs1936032	1194	ACUAAAUGUGCUGUUAGGC	137	1194	ACUAAAUGUGCUGUUAGGC	137	1212	GCCUAACAGCACAUUUAGU	1889
rs1936032	1195	CUAAAUGUGCUGUUAGGCU	138	1195	CUAAAUGUGCUGUUAGGCU	138	1213	AGCCUAACAGCACAUUUAG	1890
rs1936032	1196	UAAAUGUGCUGUUAGGCUU	139	1196	UAAAUGUGCUGUUAGGCUU	139	1214	AAGCCUAACAGCACAUUUA	1891
rs1936032	1197	AAAUGUGCUGUUAGGCUUA	140	1197	AAAUGUGCUGUUAGGCUUA	140	1215	UAAGCCUAACAGCACAUUU	1892
rs1936032	1198	AAUGUGCUGUUAGGCUUAC	141	1198	AAUGUGCUGUUAGGCUUAC	141	1216	GUAAGCCUAACAGCACAUU	1893
rs1936032	1199	AUGUGCUGUUAGGCUUACU	142	1199	AUGUGCUGUUAGGCUUACU	142	1217	AGUAAGCCUAACAGCACAU	1894
rs1936032	1200	UGUGCUGUUAGGCUUACUC	143	1200	UGUGCUGUUAGGCUUACUC	143	1218	GAGUAAGCCUAACAGCACA	1895
rs1936032	1201	GUGCUGUUAGGCUUACUCG	144	1201	GUGCUGUUAGGCUUACUCG	144	1219	CGAGUAAGCCUAACAGCAC	1896
rs1936032	1202	UGCUGUUAGGCUUACUCGU	145	1202	UGCUGUUAGGCUUACUCGU	145	1220	ACGAGUAAGCCUAACAGCA	1897
rs1936032	1203	GCUGUUAGGCUUACUCGUU	146	1203	GCUGUUAGGCUUACUCGUU	146	1221	AACGAGUAAGCCUAACAGC	1898
rs1936032	1204	CUGUUAGGCUUACUCGUUC	147	1204	CUGUUAGGCUUACUCGUUC	147	1222	GAACGAGUAAGCCUAACAG	1899
rs1936032	1205	UGUUAGGCUUACUCGUUCC	148	1205	UGUUAGGCUUACUCGUUCC	148	1223	GGAACGAGUAAGCCUAACA	1900
rs1936032	1206	GUUAGGCUUACUCGUUCCU	149	1206	GUUAGGCUUACUCGUUCCU	149	1224	AGGAACGAGUAAGCCUAAC	1901
rs1065745	1491	GCUUCUGCAAACCCUGACC	150	1491	GCUUCUGCAAACCCUGACC	150	1509	GGUCAGGGUUUGCAGAAGC	1902
rs1065745	1492	CUUCUGCAAACCCUGACCG	151	1492	CUUCUGCAAACCCUGACCG	151	1510	CGGUCAGGGUUUGCAGAAG	1903
rs1065745	1493	UUCUGCAAACCCUGACCGC	152	1493	UUCUGCAAACCCUGACCGC	152	1511	GCGGUCAGGGUUUGCAGAA	1904

rs1065745	1494	UCUGCAAACCCUGACCGCA	153	1494	UCUGCAAACCCUGACCGCA	153	1512	UGCGGUCAGGGUUUGCAGA	1905
rs1065745	1495	CUGCAAACCCUGACCGCAG	154	1495	CUGCAAACCCUGACCGCAG	154	1513	CUGCGGUCAGGGUUUGCAG	1906
rs1065745	1496	UGCAAACCCUGACCGCAGU	155	1496	UGCAAACCCUGACCGCAGU	155	1514	ACUGCGGUCAGGGUUUGCA	1907
rs1065745	1497	GCAAACCCUGACCGCAGUC	156	1497	GCAAACCCUGACCGCAGUC	156	1515	GACUGCGGUCAGGGUUUGC	1908
rs1065745	1498	CAAACCCUGACCGCAGUCG	157	1498	CAAACCCUGACCGCAGUCG	157	1516	CGACUGCGGUCAGGGUUUG	1909
rs1065745	1499	AAACCCUGACCGCAGUCGG	158	1499	AAACCCUGACCGCAGUCGG	158	1517	CCGACUGCGGUCAGGGUUU	1910
rs1065745	1500	AACCCUGACCGCAGUCGGG	159	1500	AACCCUGACCGCAGUCGGG	159	1518	CCCGACUGCGGUCAGGGUU	1911
rs1065745	1501	ACCCUGACCGCAGUCGGGG	160	1501	ACCCUGACCGCAGUCGGGG	160	1519	CCCCGACUGCGGUCAGGGU	1912
rs1065745	1502	CCCUGACCGCAGUCGGGGG	161	1502	CCCUGACCGCAGUCGGGGG	161	1520	CCCCCGACUGCGGUCAGGG	1913
rs1065745	1503	CCUGACCGCAGUCGGGGGC	162	1503	CCUGACCGCAGUCGGGGGC	162	1521	GCCCCCGACUGCGGUCAGG	1914
rs1065745	1504	CUGACCGCAGUCGGGGGCA	163	1504	CUGACCGCAGUCGGGGGCA	163	1522	UGCCCCCGACUGCGGUCAG	1915
rs1065745	1505	UGACCGCAGUCGGGGGCAU	164	1505	UGACCGCAGUCGGGGGCAU	164	1523	AUGCCCCCGACUGCGGUCA	1916
rs1065745	1506	GACCGCAGUCGGGGGCAUU	165	1506	GACCGCAGUCGGGGGCAUU	165	1524	AAUGCCCCCGACUGCGGUC	1917
rs1065745	1507	ACCGCAGUCGGGGGCAUUG	166	1507	ACCGCAGUCGGGGGCAUUG	166	1525	CAAUGCCCCCGACUGCGGU	1918
rs1065745	1508	CCGCAGUCGGGGGCAUUGG	167	1508	CCGCAGUCGGGGGCAUUGG	167	1526	CCAAUGCCCCCGACUGCGG	1919
rs1065745	1509	CGCAGUCGGGGGCAUUGGG	168	1509	CGCAGUCGGGGGCAUUGGG	168	1527	CCCAAUGCCCCCGACUGCG	1920
rs1065745	1491	GCUUCUGCAAACCCUGACU	169	1491	GCUUCUGCAAACCCUGACU	169	1509	AGUCAGGGUUUGCAGAAGC	1921
rs1065745	1492	CUUCUGCAAACCCUGACUG	170	1492	CUUCUGCAAACCCUGACUG	170	1510	CAGUCAGGGUUUGCAGAAG	1922
rs1065745	1493	UUCUGCAAACCCUGACUGC	171	1493	UUCUGCAAACCCUGACUGC	171	1511	GCAGUCAGGGUUUGCAGAA	1923
rs1065745	1494	UCUGCAAACCCUGACUGCA	172	1494	UCUGCAAACCCUGACUGCA	172	1512	UGCAGUCAGGGUUUGCAGA	1924
rs1065745	1495	CUGCAAACCCUGACUGCAG	173	1495	CUGCAAACCCUGACUGCAG	173	1513	CUGCAGUCAGGGUUUGCAG	1925
rs1065745	1496	UGCAAACCCUGACUGCAGU	174	1496	UGCAAACCCUGACUGCAGU	174	1514	ACUGCAGUCAGGGUUUGCA	1926
rs1065745	1497	GCAAACCCUGACUGCAGUC	175	1497	GCAAACCCUGACUGCAGUC	175	1515	GACUGCAGUCAGGGUUUGC	1927
rs1065745	1498	CAAACCCUGACUGCAGUCG	176	1498	CAAACCCUGACUGCAGUCG	176	1516	CGACUGCAGUCAGGGUUUG	1928
rs1065745	1499	AAACCCUGACUGCAGUCGG	177	1499	AAACCCUGACUGCAGUCGG	177	1517	CCGACUGCAGUCAGGGUUU	1929
rs1065745	1500	AACCCUGACUGCAGUCGGG	178	1500	AACCCUGACUGCAGUCGGG	178	1518	CCCGACUGCAGUCAGGGUU	1930
rs1065745	1501	ACCCUGACUGCAGUCGGGG	179	1501	ACCCUGACUGCAGUCGGGG	179	1519	CCCCGACUGCAGUCAGGGU	1931
rs1065745	1502	CCCUGACUGCAGUCGGGGG	180	1502	CCCUGACUGCAGUCGGGGG	180	1520	CCCCCGACUGCAGUCAGGG	1932
rs1065745	1503	CCUGACUGCAGUCGGGGGC	181	1503	CCUGACUGCAGUCGGGGGC	181	1521	GCCCCCGACUGCAGUCAGG	1933
rs1065745	1504	CUGACUGCAGUCGGGGGCA	182	1504	CUGACUGCAGUCGGGGGCA	182	1522	UGCCCCCGACUGCAGUCAG	1934
rs1065745	1505	UGACUGCAGUCGGGGGCAU	183	1505	UGACUGCAGUCGGGGGCAU	183	1523	AUGCCCCCGACUGCAGUCA	1935
rs1065745	1506	GACUGCAGUCGGGGGCAUU	184	1506	GACUGCAGUCGGGGGCAUU	184	1524	AAUGCCCCCGACUGCAGUC	1936
rs1065745	1507	ACUGCAGUCGGGGGCAUUG	185	1507	ACUGCAGUCGGGGGCAUUG	185	1525	CAAUGCCCCCGACUGCAGU	1937
rs1065745	1508	CUGCAGUCGGGGGCAUUGG	186	1508	CUGCAGUCGGGGGCAUUGG	186	1526	CCAAUGCCCCCGACUGCAG	1938
rs1065745	1509	UGCAGUCGGGGGCAUUGGG	187	1509	UGCAGUCGGGGGCAUUGGG	187	1527	CCCAAUGCCCCCGACUGCA	1939
rs2301367	1839	GGCGGACUCAGUGGAUCUG	188	1839	GGCGGACUCAGUGGAUCUG	188	1857	CAGAUCCACUGAGUCCGCC	1940
rs2301367	1840	GCGGACUCAGUGGAUCUGG	189	1840	GCGGACUCAGUGGAUCUGG	189	1858	CCAGAUCCACUGAGUCCGC	1941
rs2301367	1841	CGGACUCAGUGGAUCUGGC	190	1841	CGGACUCAGUGGAUCUGGC	190	1859	GCCAGAUCCACUGAGUCCG	1942
rs2301367	1842	GGACUCAGUGGAUCUGGCC	191	1842	GGACUCAGUGGAUCUGGCC	191	1860	GGCCAGAUCCACUGAGUCC	1943

rs2301367	1843	GACUCAGUGGAUCUGGCCA	192	1843	GACUCAGUGGAUCUGGCCA	192	1861	UGGCCAGAUCCACUGAGUC	1944
rs2301367	1844	ACUCAGUGGAUCUGGCCAG	193	1844	ACUCAGUGGAUCUGGCCAG	193	1862	CUGGCCAGAUCCACUGAGU	1945
rs2301367	1845	CUCAGUGGAUCUGGCCAGC	194	1845	CUCAGUGGAUCUGGCCAGC	194	1863	GCUGGCCAGAUCCACUGAG	1946
rs2301367	1846	UCAGUGGAUCUGGCCAGCU	195	1846	UCAGUGGAUCUGGCCAGCU	195	1864	AGCUGGCCAGAUCCACUGA	1947
rs2301367	1847	CAGUGGAUCUGGCCAGCUG	196	1847	CAGUGGAUCUGGCCAGCUG	196	1865	CAGCUGGCCAGAUCCACUG	1948
rs2301367	1848	AGUGGAUCUGGCCAGCUGU	197	1848	AGUGGAUCUGGCCAGCUGU	197	1866	ACAGCUGGCCAGAUCCACU	1949
rs2301367	1849	GUGGAUCUGGCCAGCUGUG	198	1849	GUGGAUCUGGCCAGCUGUG	198	1867	CACAGCUGGCCAGAUCCAC	1950
rs2301367	1850	UGGAUCUGGCCAGCUGUGA	199	1850	UGGAUCUGGCCAGCUGUGA	199	1868	UCACAGCUGGCCAGAUCCA	1951
rs2301367	1851	GGAUCUGGCCAGCUGUGAC	200	1851	GGAUCUGGCCAGCUGUGAC	200	1869	GUCACAGCUGGCCAGAUCC	1952
rs2301367	1852	GAUCUGGCCAGCUGUGACU	201	1852	GAUCUGGCCAGCUGUGACU	201	1870	AGUCACAGCUGGCCAGAUC	1953
rs2301367	1853	AUCUGGCCAGCUGUGACUU	202	1853	AUCUGGCCAGCUGUGACUU	202	1871	AAGUCACAGCUGGCCAGAU	1954
rs2301367	1854	UCUGGCCAGCUGUGACUUG	203	1854	UCUGGCCAGCUGUGACUUG	203	1872	CAAGUCACAGCUGGCCAGA	1955
rs2301367	1855	CUGGCCAGCUGUGACUUGA	204	1855	CUGGCCAGCUGUGACUUGA	204	1873	UCAAGUCACAGCUGGCCAG	1956
rs2301367	1856	UGGCCAGCUGUGACUUGAC	205	1856	UGGCCAGCUGUGACUUGAC	205	1874	GUCAAGUCACAGCUGGCCA	1957
rs2301367	1857	GGCCAGCUGUGACUUGACA	206	1857	GGCCAGCUGUGACUUGACA	206	1875	UGUCAAGUCACAGCUGGCC	1958
rs2301367	1839	GGCGGACUCAGUGGAUCUA	207	1839	GGCGGACUCAGUGGAUCUA	207	1857	UAGAUCCACUGAGUCCGCC	1959
rs2301367	1840	GCGGACUCAGUGGAUCUAG	208	1840	GCGGACUCAGUGGAUCUAG	208	1858	CUAGAUCCACUGAGUCCGC	1960
rs2301367	1841	CGGACUCAGUGGAUCUAGC	209	1841	CGGACUCAGUGGAUCUAGC	209	1859	GCUAGAUCCACUGAGUCCG	1961
rs2301367	1842	GGACUCAGUGGAUCUAGCC	210	1842	GGACUCAGUGGAUCUAGCC	210	1860	GGCUAGAUCCACUGAGUCC	1962
rs2301367	1843	GACUCAGUGGAUCUAGCCA	211	1843	GACUCAGUGGAUCUAGCCA	211	1861	UGGCUAGAUCCACUGAGUC	1963
rs2301367	1844	ACUCAGUGGAUCUAGCCAG	212	1844	ACUCAGUGGAUCUAGCCAG	212	1862	CUGGCUAGAUCCACUGAGU	1964
rs2301367	1845	CUCAGUGGAUCUAGCCAGC	213	1845	CUCAGUGGAUCUAGCCAGC	213	1863	GCUGGCUAGAUCCACUGAG	1965
rs2301367	1846	UCAGUGGAUCUAGCCAGCU	214	1846	UCAGUGGAUCUAGCCAGCU	214	1864	AGCUGGCUAGAUCCACUGA	1966
rs2301367	1847	CAGUGGAUCUAGCCAGCUG	215	1847	CAGUGGAUCUAGCCAGCUG	215	1865	CAGCUGGCUAGAUCCACUG	1967
rs2301367	1848	AGUGGAUCUAGCCAGCUGU	216	1848	AGUGGAUCUAGCCAGCUGU	216	1866	ACAGCUGGCUAGAUCCACU	1968
rs2301367	1849	GUGGAUCUAGCCAGCUGUG	217	1849	GUGGAUCUAGCCAGCUGUG	217	1867	CACAGCUGGCUAGAUCCAC	1969
rs2301367	1850	UGGAUCUAGCCAGCUGUGA	218	1850	UGGAUCUAGCCAGCUGUGA	218	1868	UCACAGCUGGCUAGAUCCA	1970
rs2301367	1851	GGAUCUAGCCAGCUGUGAC	219	1851	GGAUCUAGCCAGCUGUGAC	219	1869	GUCACAGCUGGCUAGAUCC	1971
rs2301367	1852	GAUCUAGCCAGCUGUGACU	220	1852	GAUCUAGCCAGCUGUGACU	220	1870	AGUCACAGCUGGCUAGAUC	1972
rs2301367	1853	AUCUAGCCAGCUGUGACUU	221	1853	AUCUAGCCAGCUGUGACUU	221	1871	AAGUCACAGCUGGCUAGAU	1973
rs2301367	1854	UCUAGCCAGCUGUGACUUG	222	1854	UCUAGCCAGCUGUGACUUG	222	1872	CAAGUCACAGCUGGCUAGA	1974
rs2301367	1855	CUAGCCAGCUGUGACUUGA	223	1855	CUAGCCAGCUGUGACUUGA	223	1873	UCAAGUCACAGCUGGCUAG	1975
rs2301367	1856	UAGCCAGCUGUGACUUGAC	224	1856	UAGCCAGCUGUGACUUGAC	224	1874	GUCAAGUCACAGCUGGCUA	1976
rs2301367	1857	AGCCAGCUGUGACUUGACA	225	1857	AGCCAGCUGUGACUUGACA	225	1875	UGUCAAGUCACAGCUGGCU	1977
rs363075	2980	GCAGAAAACUUACACAGAG	226	2980	GCAGAAAACUUACACAGAG	226	2998	CUCUGUGUAAGUUUUCUGC	1978
rs363075	2981	CAGAAAACUUACACAGAGG	227	2981	CAGAAAACUUACACAGAGG	227	2999	CCUCUGUGUAAGUUUUCUG	1979
rs363075	2982	AGAAAACUUACACAGAGGG	228	2982	AGAAAACUUACACAGAGGG	228	3000	CCCUCUGUGUAAGUUUUCU	1980
rs363075	2983	GAAAACUUACACAGAGGGG	229	2983	GAAAACUUACACAGAGGGG	229	3001	CCCCUCUGUGUAAGUUUUC	1981
rs363075	2984	AAAACUUACACAGAGGGGC	230	2984	AAAACUUACACAGAGGGGC	230	3002	GCCCCUCUGUGUAAGUUUU	1982

rs363075	2985	AAACUUACACAGAGGGGCU	231	2985	AAACUUACACAGAGGGGCU	231	3003	AGCCCCUCUGUGUAAGUUU	1983
rs363075	2986	AACUUACACAGAGGGGCUC	232	2986	AACUUACACAGAGGGGCUC	232	3004	GAGCCCCUCUGUGUAAGUU	1984
rs363075	2987	ACUUACACAGAGGGGCUCA	233	2987	ACUUACACAGAGGGGCUCA	233	3005	UGAGCCCCUCUGUGUAAGU	1985
rs363075	2988	CUUACACAGAGGGGCUCAU	234	2988	CUUACACAGAGGGGCUCAU	234	3006	AUGAGCCCCUCUGUGUAAG	1986
rs363075	2989	UUACACAGAGGGGCUCAUC	235	2989	UUACACAGAGGGGCUCAUC	235	3007	GAUGAGCCCCUCUGUGUAA	1987
rs363075	2990	UACACAGAGGGGCUCAUCA	236	2990	UACACAGAGGGGCUCAUCA	236	3008	UGAUGAGCCCCUCUGUGUA	1988
rs363075	2991	ACACAGAGGGGCUCAUCAU	237	2991	ACACAGAGGGGCUCAUCAU	237	3009	AUGAUGAGCCCCUCUGUGU	1989
rs363075	2992	CACAGAGGGGCUCAUCAUU	238	2992	CACAGAGGGGCUCAUCAUU	238	3010	AAUGAUGAGCCCCUCUGUG	1990
rs363075	2993	ACAGAGGGGCUCAUCAUUA	239	2993	ACAGAGGGGCUCAUCAUUA	239	3011	UAAUGAUGAGCCCCUCUGU	1991
rs363075	2994	CAGAGGGGCUCAUCAUUAU	240	2994	CAGAGGGGCUCAUCAUUAU	240	3012	AUAAUGAUGAGCCCCUCUG	1992
rs363075	2995	AGAGGGGCUCAUCAUUAUA	241	2995	AGAGGGGCUCAUCAUUAUA	241	3013	UAUAAUGAUGAGCCCCUCU	1993
rs363075	2996	GAGGGGCUCAUCAUUAUAC	242	2996	GAGGGGCUCAUCAUUAUAC	242	3014	GUAUAAUGAUGAGCCCCUC	1994
rs363075	2997	AGGGGCUCAUCAUUAUACA	243	2997	AGGGGCUCAUCAUUAUACA	243	3015	UGUAUAAUGAUGAGCCCCU	1995
rs363075	2998	GGGGCUCAUCAUUAUACAG	244	2998	GGGGCUCAUCAUUAUACAG	244	3016	CUGUAUAAUGAUGAGCCCC	1996
rs363075	2980	GCAGAAAACUUACACAGAA	245	2980	GCAGAAAACUUACACAGAA	245	2998	UUCUGUGUAAGUUUUCUGC	1997
rs363075	2981	CAGAAAACUUACACAGAAG	246	2981	CAGAAAACUUACACAGAAG	246	2999	CUUCUGUGUAAGUUUUCUG	1998
rs363075	2982	AGAAAACUUACACAGAAGG	247	2982	AGAAAACUUACACAGAAGG	247	3000	CCUUCUGUGUAAGUUUUCU	1999
rs363075	2983	GAAAACUUACACAGAAGGG	248	2983	GAAAACUUACACAGAAGGG	248	3001	CCCUUCUGUGUAAGUUUUC	2000
rs363075	2984	AAAACUUACACAGAAGGGC	249	2984	AAAACUUACACAGAAGGGC	249	3002	GCCCUUCUGUGUAAGUUUU	2001
rs363075	2985	AAACUUACACAGAAGGGCU	250	2985	AAACUUACACAGAAGGGCU	250	3003	AGCCCUUCUGUGUAAGUUU	2002
rs363075	2986	AACUUACACAGAAGGGCUC	251	2986	AACUUACACAGAAGGGCUC	251	3004	GAGCCCUUCUGUGUAAGUU	2003
rs363075	2987	ACUUACACAGAAGGGCUCA	252	2987	ACUUACACAGAAGGGCUCA	252	3005	UGAGCCCUUCUGUGUAAGU	2004
rs363075	2988	CUUACACAGAAGGGCUCAU	253	2988	CUUACACAGAAGGGCUCAU	253	3006	AUGAGCCCUUCUGUGUAAG	2005
rs363075	2989	UUACACAGAAGGGCUCAUC	254	2989	UUACACAGAAGGGCUCAUC	254	3007	GAUGAGCCCUUCUGUGUAA	2006
rs363075	2990	UACACAGAAGGGCUCAUCA	255	2990	UACACAGAAGGGCUCAUCA	255	3008	UGAUGAGCCCUUCUGUGUA	2007
rs363075	2991	ACACAGAAGGGCUCAUCAU	256	2991	ACACAGAAGGGCUCAUCAU	256	3009	AUGAUGAGCCCUUCUGUGU	2008
rs363075	2992	CACAGAAGGGCUCAUCAUU	257	2992	CACAGAAGGGCUCAUCAUU	257	3010	AAUGAUGAGCCCUUCUGUG	2009
rs363075	2993	ACAGAAGGGCUCAUCAUUA	258	2993	ACAGAAGGGCUCAUCAUUA	258	3011	UAAUGAUGAGCCCUUCUGU	2010
rs363075	2994	CAGAAGGGCUCAUCAUUAU	259	2994	CAGAAGGGCUCAUCAUUAU	259	3012	AUAAUGAUGAGCCCUUCUG	2011
rs363075	2995	AGAAGGGCUCAUCAUUAUA	260	2995	AGAAGGGCUCAUCAUUAUA	260	3013	UAUAAUGAUGAGCCCUUCU	2012
rs363075	2996	GAAGGGCUCAUCAUUAUAC	261	2996	GAAGGGCUCAUCAUUAUAC	261	3014	GUAUAAUGAUGAGCCCUUC	2013
rs363075	2997	AAGGGCUCAUCAUUAUACA	262	2997	AAGGGCUCAUCAUUAUACA	262	3015	UGUAUAAUGAUGAGCCCUU	2014
rs363075	2998	AGGGCUCAUCAUUAUACAG	263	2998	AGGGCUCAUCAUUAUACAG	263	3016	CUGUAUAAUGAUGAGCCCU	2015
rs1065746	3547	UCAGCUUGGUUCCCAUUGG	264	3547	UCAGCUUGGUUCCCAUUGG	264	3565	CCAAUGGGAACCAAGCUGA	2016
rs1065746	3548	CAGCUUGGUUCCCAUUGGA	265	3548	CAGCUUGGUUCCCAUUGGA	265	3566	UCCAAUGGGAACCAAGCUG	2017
rs1065746	3549	AGCUUGGUUCCCAUUGGAU	266	3549	AGCUUGGUUCCCAUUGGAU	266	3567	AUCCAAUGGGAACCAAGCU	2018
rs1065746	3550	GCUUGGUUCCCAUUGGAUC	267	3550	GCUUGGUUCCCAUUGGAUC	267	3568	GAUCCAAUGGGAACCAAGC	2019
rs1065746	3551	CUUGGUUCCCAUUGGAUCU	268	3551	CUUGGUUCCCAUUGGAUCU	268	3569	AGAUCCAAUGGGAACCAAG	2020
rs1065746	3552	UUGGUUCCCAUUGGAUCUC	269	3552	UUGGUUCCCAUUGGAUCUC	269	3570	GAGAUCCAAUGGGAACCAA	2021

rs1065746	3553	UGGUUCCCAUUGGAUCUCU	270	3553	UGGUUCCCAUUGGAUCUCU	270	3571	AGAGAUCCAAUGGGAACCA	2022
rs1065746	3554	GGUUCCCAUUGGAUCUCUC	271	3554	GGUUCCCAUUGGAUCUCUC	271	3572	GAGAGAUCCAAUGGGAACC	2023
rs1065746	3555	GUUCCCAUUGGAUCUCUCA	272	3555	GUUCCCAUUGGAUCUCUCA	272	3573	UGAGAGAUCCAAUGGGAAC	2024
rs1065746	3556	UUCCCAUUGGAUCUCUCAG	273	3556	UUCCCAUUGGAUCUCUCAG	273	3574	CUGAGAGAUCCAAUGGGAA	2025
rs1065746	3557	UCCCAUUGGAUCUCUCAGC	274	3557	UCCCAUUGGAUCUCUCAGC	274	3575	GCUGAGAGAUCCAAUGGGA	2026
rs1065746	3558	CCCAUUGGAUCUCUCAGCC	275	3558	CCCAUUGGAUCUCUCAGCC	275	3576	GGCUGAGAGAUCCAAUGGG	2027
rs1065746	3559	CCAUUGGAUCUCUCAGCCC	276	3559	CCAUUGGAUCUCUCAGCCC	276	3577	GGGCUGAGAGAUCCAAUGG	2028
rs1065746	3560	CAUUGGAUCUCUCAGCCCA	277	3560	CAUUGGAUCUCUCAGCCCA	277	3578	UGGGCUGAGAGAUCCAAUG	2029
rs1065746	3561	AUUGGAUCUCUCAGCCCAU	278	3561	AUUGGAUCUCUCAGCCCAU	278	3579	AUGGGCUGAGAGAUCCAAU	2030
rs1065746	3562	UUGGAUCUCUCAGCCCAUC	279	3562	UUGGAUCUCUCAGCCCAUC	279	3580	GAUGGGCUGAGAGAUCCAA	2031
rs1065746	3563	UGGAUCUCUCAGCCCAUCA	280	3563	UGGAUCUCUCAGCCCAUCA	280	3581	UGAUGGGCUGAGAGAUCCA	2032
rs1065746	3564	GGAUCUCUCAGCCCAUCAA	281	3564	GGAUCUCUCAGCCCAUCAA	281	3582	UUGAUGGGCUGAGAGAUCC	2033
rs1065746	3565	GAUCUCUCAGCCCAUCAAG	282	3565	GAUCUCUCAGCCCAUCAAG	282	3583	CUUGAUGGGCUGAGAGAUC	2034
rs1065746	3547	UCAGCUUGGUUCCCAUUGA	283	3547	UCAGCUUGGUUCCCAUUGA	283	3565	UCAAUGGGAACCAAGCUGA	2035
rs1065746	3548	CAGCUUGGUUCCCAUUGAA	284	3548	CAGCUUGGUUCCCAUUGAA	284	3566	UUCAAUGGGAACCAAGCUG	2036
rs1065746	3549	AGCUUGGUUCCCAUUGAAU	285	3549	AGCUUGGUUCCCAUUGAAU	285	3567	AUUCAAUGGGAACCAAGCU	2037
rs1065746	3550	GCUUGGUUCCCAUUGAAUC	286	3550	GCUUGGUUCCCAUUGAAUC	286	3568	GAUUCAAUGGGAACCAAGC	2038
rs1065746	3551	CUUGGUUCCCAUUGAAUCU	287	3551	CUUGGUUCCCAUUGAAUCU	287	3569	AGAUUCAAUGGGAACCAAG	2039
rs1065746	3552	UUGGUUCCCAUUGAAUCUC	288	3552	UUGGUUCCCAUUGAAUCUC	288	3570	GAGAUUCAAUGGGAACCAA	2040
rs1065746	3553	UGGUUCCCAUUGAAUCUCU	289	3553	UGGUUCCCAUUGAAUCUCU	289	3571	AGAGAUUCAAUGGGAACCA	2041
rs1065746	3554	GGUUCCCAUUGAAUCUCUC	290	3554	GGUUCCCAUUGAAUCUCUC	290	3572	GAGAGAUUCAAUGGGAACC	2042
rs1065746	3555	GUUCCCAUUGAAUCUCUCA	291	3555	GUUCCCAUUGAAUCUCUCA	291	3573	UGAGAGAUUCAAUGGGAAC	2043
rs1065746	3556	UUCCCAUUGAAUCUCUCAG	292	3556	UUCCCAUUGAAUCUCUCAG	292	3574	CUGAGAGAUUCAAUGGGAA	2044
rs1065746	3557	UCCCAUUGAAUCUCUCAGC	293	3557	UCCCAUUGAAUCUCUCAGC	293	3575	GCUGAGAGAUUCAAUGGGA	2045
rs1065746	3558	CCCAUUGAAUCUCUCAGCC	294	3558	CCCAUUGAAUCUCUCAGCC	294	3576	GGCUGAGAGAUUCAAUGGG	2046
rs1065746	3559	CCAUUGAAUCUCUCAGCCC	295	3559	CCAUUGAAUCUCUCAGCCC	295	3577	GGGCUGAGAGAUUCAAUGG	2047
rs1065746	3560	CAUUGAAUCUCUCAGCCCA	296	3560	CAUUGAAUCUCUCAGCCCA	296	3578	UGGGCUGAGAGAUUCAAUG	2048
rs1065746	3561	AUUGAAUCUCUCAGCCCAU	297	3561	AUUGAAUCUCUCAGCCCAU	297	3579	AUGGGCUGAGAGAUUCAAU	2049
rs1065746	3562	UUGAAUCUCUCAGCCCAUC	298	3562	UUGAAUCUCUCAGCCCAUC	298	3580	GAUGGGCUGAGAGAUUCAA	2050
rs1065746	3563	UGAAUCUCUCAGCCCAUCA	299	3563	UGAAUCUCUCAGCCCAUCA	299	3581	UGAUGGGCUGAGAGAUUCA	2051
rs1065746	3564	GAAUCUCUCAGCCCAUCAA	300	3564	GAAUCUCUCAGCCCAUCAA	300	3582	UUGAUGGGCUGAGAGAUUC	2052
rs1065746	3565	AAUCUCUCAGCCCAUCAAG	301	3565	AAUCUCUCAGCCCAUCAAG	301	3583	CUUGAUGGGCUGAGAGAUU	2053
rs1065746	3547	UCAGCUUGGUUCCCAUUGC	302	3547	UCAGCUUGGUUCCCAUUGC	302	3565	GCAAUGGGAACCAAGCUGA	2054
rs1065746	3548	CAGCUUGGUUCCCAUUGCA	303	3548	CAGCUUGGUUCCCAUUGCA	303	3566	UGCAAUGGGAACCAAGCUG	2055
rs1065746	3549	AGCUUGGUUCCCAUUGCAU	304	3549	AGCUUGGUUCCCAUUGCAU	304	3567	AUGCAAUGGGAACCAAGCU	2056
rs1065746	3550	GCUUGGUUCCCAUUGCAUC	305	3550	GCUUGGUUCCCAUUGCAUC	305	3568	GAUGCAAUGGGAACCAAGC	2057
rs1065746	3551	CUUGGUUCCCAUUGCAUCU	306	3551	CUUGGUUCCCAUUGCAUCU	306	3569	AGAUGCAAUGGGAACCAAG	2058
rs1065746	3552	UUGGUUCCCAUUGCAUCUC	307	3552	UUGGUUCCCAUUGCAUCUC	307	3570	GAGAUGCAAUGGGAACCAA	2059
rs1065746	3553	UGGUUCCCAUUGCAUCUCU	308	3553	UGGUUCCCAUUGCAUCUCU	308	3571	AGAGAUGCAAUGGGAACCA	2060

rs1065746	3554	GGUUCCCAUUGCAUCUCUC	309	3554	GGUUCCCAUUGCAUCUCUC	309	3572	GAGAGAUGCAAUGGGAACC	2061
rs1065746	3555	GUUCCCAUUGCAUCUCUCA	310	3555	GUUCCCAUUGCAUCUCUCA	310	3573	UGAGAGAUGCAAUGGGAAC	2062
rs1065746	3556	UUCCCAUUGCAUCUCUCAG	311	3556	UUCCCAUUGCAUCUCUCAG	311	3574	CUGAGAGAUGCAAUGGGAA	2063
rs1065746	3557	UCCCAUUGCAUCUCUCAGC	312	3557	UCCCAUUGCAUCUCUCAGC	312	3575	GCUGAGAGAUGCAAUGGGA	2064
rs1065746	3558	CCCAUUGCAUCUCUCAGCC	313	3558	CCCAUUGCAUCUCUCAGCC	313	3576	GGCUGAGAGAUGCAAUGGG	2065
rs1065746	3559	CCAUUGCAUCUCUCAGCCC	314	3559	CCAUUGCAUCUCUCAGCCC	314	3577	GGGCUGAGAGAUGCAAUGG	2066
rs1065746	3560	CAUUGCAUCUCUCAGCCCA	315	3560	CAUUGCAUCUCUCAGCCCA	315	3578	UGGGCUGAGAGAUGCAAUG	2067
rs1065746	3561	AUUGCAUCUCUCAGCCCAU	316	3561	AUUGCAUCUCUCAGCCCAU	316	3579	AUGGGCUGAGAGAUGCAAU	2068
rs1065746	3562	UUGCAUCUCUCAGCCCAUC	317	3562	UUGCAUCUCUCAGCCCAUC	317	3580	GAUGGGCUGAGAGAUGCAA	2069
rs1065746	3563	UGCAUCUCUCAGCCCAUCA	318	3563	UGCAUCUCUCAGCCCAUCA	318	3581	UGAUGGGCUGAGAGAUGCA	2070
rs1065746	3564	GCAUCUCUCAGCCCAUCAA	319	3564	GCAUCUCUCAGCCCAUCAA	319	3582	UUGAUGGGCUGAGAGAUGC	2071
rs1065746	3565	CAUCUCUCAGCCCAUCAAG	320	3565	CAUCUCUCAGCCCAUCAAG	320	3583	CUUGAUGGGCUGAGAGAUG	2072
rs1065747	3647	GGGCCUCUGAAGAAGAAGC	321	3647	GGGCCUCUGAAGAAGAAGC	321	3665	GCUUCUUCUUCAGAGGCCC	2073
rs1065747	3648	GGCCUCUGAAGAAGAAGCC	322	3648	GGCCUCUGAAGAAGAAGCC	322	3666	GGCUUCUUCUUCAGAGGCC	2074
rs1065747	3649	GCCUCUGAAGAAGAAGCCA	323	3649	GCCUCUGAAGAAGAAGCCA	323	3667	UGGCUUCUUCUUCAGAGGC	2075
rs1065747	3650	CCUCUGAAGAAGAAGCCAA	324	3650	CCUCUGAAGAAGAAGCCAA	324	3668	UUGGCUUCUUCUUCAGAGG	2076
rs1065747	3651	CUCUGAAGAAGAAGCCAAC	325	3651	CUCUGAAGAAGAAGCCAAC	325	3669	GUUGGCUUCUUCUUCAGAG	2077
rs1065747	3652	UCUGAAGAAGAAGCCAACC	326	3652	UCUGAAGAAGAAGCCAACC	326	3670	GGUUGGCUUCUUCUUCAGA	2078
rs1065747	3653	CUGAAGAAGAAGCCAACCC	327	3653	CUGAAGAAGAAGCCAACCC	327	3671	GGGUUGGCUUCUUCUUCAG	2079
rs1065747	3654	UGAAGAAGAAGCCAACCCA	328	3654	UGAAGAAGAAGCCAACCCA	328	3672	UGGGUUGGCUUCUUCUUCA	2080
rs1065747	3655	GAAGAAGAAGCCAACCCAG	329	3655	GAAGAAGAAGCCAACCCAG	329	3673	CUGGGUUGGCUUCUUCUUC	2081
rs1065747	3656	AAGAAGAAGCCAACCCAGC	330	3656	AAGAAGAAGCCAACCCAGC	330	3674	GCUGGGUUGGCUUCUUCUU	2082
rs1065747	3657	AGAAGAAGCCAACCCAGCA	331	3657	AGAAGAAGCCAACCCAGCA	331	3675	UGCUGGGUUGGCUUCUUCU	2083
rs1065747	3658	GAAGAAGCCAACCCAGCAG	332	3658	GAAGAAGCCAACCCAGCAG	332	3676	CUGCUGGGUUGGCUUCUUC	2084
rs1065747	3659	AAGAAGCCAACCCAGCAGC	333	3659	AAGAAGCCAACCCAGCAGC	333	3677	GCUGCUGGGUUGGCUUCUU	2085
rs1065747	3660	AGAAGCCAACCCAGCAGCC	334	3660	AGAAGCCAACCCAGCAGCC	334	3678	GGCUGCUGGGUUGGCUUCU	2086
rs1065747	3661	GAAGCCAACCCAGCAGCCA	335	3661	GAAGCCAACCCAGCAGCCA	335	3679	UGGCUGCUGGGUUGGCUUC	2087
rs1065747	3662	AAGCCAACCCAGCAGCCAC	336	3662	AAGCCAACCCAGCAGCCAC	336	3680	GUGGCUGCUGGGUUGGCUU	2088
rs1065747	3663	AGCCAACCCAGCAGCCACC	337	3663	AGCCAACCCAGCAGCCACC	337	3681	GGUGGCUGCUGGGUUGGCU	2089
rs1065747	3664	GCCAACCCAGCAGCCACCA	338	3664	GCCAACCCAGCAGCCACCA	338	3682	UGGUGGCUGCUGGGUUGGC	2090
rs1065747	3665	CCAACCCAGCAGCCACCAA	339	3665	CCAACCCAGCAGCCACCAA	339	3683	UUGGUGGCUGCUGGGUUGG	2091
rs1065747	3647	GGGCCUCUGAAGAAGAAGG	340	3647	GGGCCUCUGAAGAAGAAGG	340	3665	CCUUCUUCUUCAGAGGCCC	2092
rs1065747	3648	GGCCUCUGAAGAAGAAGGC	341	3648	GGCCUCUGAAGAAGAAGGC	341	3666	GCCUUCUUCUUCAGAGGCC	2093
rs1065747	3649	GCCUCUGAAGAAGAAGGCA	342	3649	GCCUCUGAAGAAGAAGGCA	342	3667	UGCCUUCUUCUUCAGAGGC	2094
rs1065747	3650	CCUCUGAAGAAGAAGGCAA	343	3650	CCUCUGAAGAAGAAGGCAA	343	3668	UUGCCUUCUUCUUCAGAGG	2095
rs1065747	3651	CUCUGAAGAAGAAGGCAAC	344	3651	CUCUGAAGAAGAAGGCAAC	344	3669	GUUGCCUUCUUCUUCAGAG	2096
rs1065747	3652	UCUGAAGAAGAAGGCAACC	345	3652	UCUGAAGAAGAAGGCAACC	345	3670	GGUUGCCUUCUUCUUCAGA	2097
rs1065747	3653	CUGAAGAAGAAGGCAACCC	346	3653	CUGAAGAAGAAGGCAACCC	346	3671	GGGUUGCCUUCUUCUUCAG	2098
rs1065747	3654	UGAAGAAGAAGGCAACCCA	347	3654	UGAAGAAGAAGGCAACCCA	347	3672	UGGGUUGCCUUCUUCUUCA	2099

rs1065747	3655	GAAGAAGAAGGCAACCCAG	348	3655	GAAGAAGAAGGCAACCCAG	348	3673	CUGGGUUGCCUUCUUCUUC	2100
rs1065747	3656	AAGAAGAAGGCAACCCAGC	349	3656	AAGAAGAAGGCAACCCAGC	349	3674	GCUGGGUUGCCUUCUUCUU	2101
rs1065747	3657	AGAAGAAGGCAACCCAGCA	350	3657	AGAAGAAGGCAACCCAGCA	350	3675	UGCUGGGUUGCCUUCUUCU	2102
rs1065747	3658	GAAGAAGGCAACCCAGCAG	351	3658	GAAGAAGGCAACCCAGCAG	351	3676	CUGCUGGGUUGCCUUCUUC	2103
rs1065747	3659	AAGAAGGCAACCCAGCAGC	352	3659	AAGAAGGCAACCCAGCAGC	352	3677	GCUGCUGGGUUGCCUUCUU	2104
rs1065747	3660	AGAAGGCAACCCAGCAGCC	353	3660	AGAAGGCAACCCAGCAGCC	353	3678	GGCUGCUGGGUUGCCUUCU	2105
rs1065747	3661	GAAGGCAACCCAGCAGCCA	354	3661	GAAGGCAACCCAGCAGCCA	354	3679	UGGCUGCUGGGUUGCCUUC	2106
rs1065747	3662	AAGGCAACCCAGCAGCCAC	355	3662	AAGGCAACCCAGCAGCCAC	355	3680	GUGGCUGCUGGGUUGCCUU	2107
rs1065747	3663	AGGCAACCCAGCAGCCACC	356	3663	AGGCAACCCAGCAGCCACC	356	3681	GGUGGCUGCUGGGUUGCCU	2108
rs1065747	3664	GGCAACCCAGCAGCCACCA	357	3664	GGCAACCCAGCAGCCACCA	357	3682	UGGUGGCUGCUGGGUUGCC	2109
rs1065747	3665	GCAACCCAGCAGCCACCAA	358	3665	GCAACCCAGCAGCCACCAA	358	3683	UUGGUGGCUGCUGGGUUGC	2110
rs2530588	3803	CUGGACCCGCAAUAAAGGC	359	3803	CUGGACCCGCAAUAAAGGC	359	3821	GCCUUUAUUGCGGGUCCAG	2111
rs2530588	3804	UGGACCCGCAAUAAAGGCA	360	3804	UGGACCCGCAAUAAAGGCA	360	3822	UGCCUUUAUUGCGGGUCCA	2112
rs2530588	3805	GGACCCGCAAUAAAGGCAG	361	3805	GGACCCGCAAUAAAGGCAG	361	3823	CUGCCUUUAUUGCGGGUCC	2113
rs2530588	3806	GACCCGCAAUAAAGGCAGC	362	3806	GACCCGCAAUAAAGGCAGC	362	3824	GCUGCCUUUAUUGCGGGUC	2114
rs2530588	3807	ACCCGCAAUAAAGGCAGCC	363	3807	ACCCGCAAUAAAGGCAGCC	363	3825	GGCUGCCUUUAUUGCGGGU	2115
rs2530588	3808	CCCGCAAUAAAGGCAGCCU	364	3808	CCCGCAAUAAAGGCAGCCU	364	3826	AGGCUGCCUUUAUUGCGGG	2116
rs2530588	3809	CCGCAAUAAAGGCAGCCUU	365	3809	CCGCAAUAAAGGCAGCCUU	365	3827	AAGGCUGCCUUUAUUGCGG	2117
rs2530588	3810	CGCAAUAAAGGCAGCCUUG	366	3810	CGCAAUAAAGGCAGCCUUG	366	3828	CAAGGCUGCCUUUAUUGCG	2118
rs2530588	3811	GCAAUAAAGGCAGCCUUGC	367	3811	GCAAUAAAGGCAGCCUUGC	367	3829	GCAAGGCUGCCUUUAUUGC	2119
rs2530588	3812	CAAUAAAGGCAGCCUUGCC	368	3812	CAAUAAAGGCAGCCUUGCC	368	3830	GGCAAGGCUGCCUUUAUUG	2120
rs2530588	3813	AAUAAAGGCAGCCUUGCCU	369	3813	AAUAAAGGCAGCCUUGCCU	369	3831	AGGCAAGGCUGCCUUUAUU	2121
rs2530588	3814	AUAAAGGCAGCCUUGCCUU	370	3814	AUAAAGGCAGCCUUGCCUU	370	3832	AAGGCAAGGCUGCCUUUAU	2122
rs2530588	3815	UAAAGGCAGCCUUGCCUUC	371	3815	UAAAGGCAGCCUUGCCUUC	371	3833	GAAGGCAAGGCUGCCUUUA	2123
rs2530588	3816	AAAGGCAGCCUUGCCUUCU	372	3816	AAAGGCAGCCUUGCCUUCU	372	3834	AGAAGGCAAGGCUGCCUUU	2124
rs2530588	3817	AAGGCAGCCUUGCCUUCUC	373	3817	AAGGCAGCCUUGCCUUCUC	373	3835	GAGAAGGCAAGGCUGCCUU	2125
rs2530588	3818	AGGCAGCCUUGCCUUCUCU	374	3818	AGGCAGCCUUGCCUUCUCU	374	3836	AGAGAAGGCAAGGCUGCCU	2126
rs2530588	3819	GGCAGCCUUGCCUUCUCUA	375	3819	GGCAGCCUUGCCUUCUCUA	375	3837	UAGAGAAGGCAAGGCUGCC	2127
rs2530588	3820	GCAGCCUUGCCUUCUCUAA	376	3820	GCAGCCUUGCCUUCUCUAA	376	3838	UUAGAGAAGGCAAGGCUGC	2128
rs2530588	3821	CAGCCUUGCCUUCUCUAAC	377	3821	CAGCCUUGCCUUCUCUAAC	377	3839	GUUAGAGAAGGCAAGGCUG	2129
rs2530588	3803	CUGGACCCGCAAUAAAGGA	378	3803	CUGGACCCGCAAUAAAGGA	378	3821	UCCUUUAUUGCGGGUCCAG	2130
rs2530588	3804	UGGACCCGCAAUAAAGGAA	379	3804	UGGACCCGCAAUAAAGGAA	379	3822	UUCCUUUAUUGCGGGUCCA	2131
rs2530588	3805	GGACCCGCAAUAAAGGAAG	380	3805	GGACCCGCAAUAAAGGAAG	380	3823	CUUCCUUUAUUGCGGGUCC	2132
rs2530588	3806	GACCCGCAAUAAAGGAAGC	381	3806	GACCCGCAAUAAAGGAAGC	381	3824	GCUUCCUUUAUUGCGGGUC	2133
rs2530588	3807	ACCCGCAAUAAAGGAAGCC	382	3807	ACCCGCAAUAAAGGAAGCC	382	3825	GGCUUCCUUUAUUGCGGGU	2134
rs2530588	3808	CCCGCAAUAAAGGAAGCCU	383	3808	CCCGCAAUAAAGGAAGCCU	383	3826	AGGCUUCCUUUAUUGCGGG	2135
rs2530588	3809	CCGCAAUAAAGGAAGCCUU	384	3809	CCGCAAUAAAGGAAGCCUU	384	3827	AAGGCUUCCUUUAUUGCGG	2136
rs2530588	3810	CGCAAUAAAGGAAGCCUUG	385	3810	CGCAAUAAAGGAAGCCUUG	385	3828	CAAGGCUUCCUUUAUUGCG	2137
rs2530588	3811	GCAAUAAAGGAAGCCUUGC	386	3811	GCAAUAAAGGAAGCCUUGC	386	3829	GCAAGGCUUCCUUUAUUGC	2138

rs2530588	3812	CAAUAAAGGAAGCCUUGCC	387	3812	CAAUAAAGGAAGCCUUGCC	387	3830	GGCAAGGCUUCCUUUAUUG	2139
rs2530588	3813	AAUAAAGGAAGCCUUGCCU	388	3813	AAUAAAGGAAGCCUUGCCU	388	3831	AGGCAAGGCUUCCUUUAUU	2140
rs2530588	3814	AUAAAGGAAGCCUUGCCUU	389	3814	AUAAAGGAAGCCUUGCCUU	389	3832	AAGGCAAGGCUUCCUUUAU	2141
rs2530588	3815	UAAAGGAAGCCUUGCCUUC	390	3815	UAAAGGAAGCCUUGCCUUC	390	3833	GAAGGCAAGGCUUCCUUUA	2142
rs2530588	3816	AAAGGAAGCCUUGCCUUCU	391	3816	AAAGGAAGCCUUGCCUUCU	391	3834	AGAAGGCAAGGCUUCCUUU	2143
rs2530588	3817	AAGGAAGCCUUGCCUUCUC	392	3817	AAGGAAGCCUUGCCUUCUC	392	3835	GAGAAGGCAAGGCUUCCUU	2144
rs2530588	3818	AGGAAGCCUUGCCUUCUCU	393	3818	AGGAAGCCUUGCCUUCUCU	393	3836	AGAGAAGGCAAGGCUUCCU	2145
rs2530588	3819	GGAAGCCUUGCCUUCUCUA	394	3819	GGAAGCCUUGCCUUCUCUA	394	3837	UAGAGAAGGCAAGGCUUCC	2146
rs2530588	3820	GAAGCCUUGCCUUCUCUAA	395	3820	GAAGCCUUGCCUUCUCUAA	395	3838	UUAGAGAAGGCAAGGCUUC	2147
rs2530588	3821	AAGCCUUGCCUUCUCUAAC	396	3821	AAGCCUUGCCUUCUCUAAC	396	3839	GUUAGAGAAGGCAAGGCUU	2148
rs3025843	3822	AGCCUUGCCUUCUCUAACA	397	3822	AGCCUUGCCUUCUCUAACA	397	3840	UGUUAGAGAAGGCAAGGCU	2149
rs3025843	3823	GCCUUGCCUUCUCUAACAA	398	3823	GCCUUGCCUUCUCUAACAA	398	3841	UUGUUAGAGAAGGCAAGGC	2150
rs3025843	3824	CCUUGCCUUCUCUAACAAA	399	3824	CCUUGCCUUCUCUAACAAA	399	3842	UUUGUUAGAGAAGGCAAGG	2151
rs3025843	3825	CUUGCCUUCUCUAACAAAC	400	3825	CUUGCCUUCUCUAACAAAC	400	3843	GUUUGUUAGAGAAGGCAAG	2152
rs3025843	3826	UUGCCUUCUCUAACAAACC	401	3826	UUGCCUUCUCUAACAAACC	401	3844	GGUUUGUUAGAGAAGGCAA	2153
rs3025843	3827	UGCCUUCUCUAACAAACCC	402	3827	UGCCUUCUCUAACAAACCC	402	3845	GGGUUUGUUAGAGAAGGCA	2154
rs3025843	3828	GCCUUCUCUAACAAACCCC	403	3828	GCCUUCUCUAACAAACCCC	403	3846	GGGGUUUGUUAGAGAAGGC	2155
rs3025843	3829	CCUUCUCUAACAAACCCCC	404	3829	CCUUCUCUAACAAACCCCC	404	3847	GGGGGUUUGUUAGAGAAGG	2156
rs3025843	3830	CUUCUCUAACAAACCCCCC	405	3830	CUUCUCUAACAAACCCCCC	405	3848	GGGGGGUUUGUUAGAGAAG	2157
rs3025843	3831	UUCUCUAACAAACCCCCCU	406	3831	UUCUCUAACAAACCCCCCU	406	3849	AGGGGGGUUUGUUAGAGAA	2158
rs3025843	3832	UCUCUAACAAACCCCCCUU	407	3832	UCUCUAACAAACCCCCCUU	407	3850	AAGGGGGGUUUGUUAGAGA	2159
rs3025843	3833	CUCUAACAAACCCCCCUUC	408	3833	CUCUAACAAACCCCCCUUC	408	3851	GAAGGGGGGUUUGUUAGAG	2160
rs3025843	3834	UCUAACAAACCCCCCUUCU	409	3834	UCUAACAAACCCCCCUUCU	409	3852	AGAAGGGGGGUUUGUUAGA	2161
rs3025843	3835	CUAACAAACCCCCCUUCUC	410	3835	CUAACAAACCCCCCUUCUC	410	3853	GAGAAGGGGGGUUUGUUAG	2162
rs3025843	3836	UAACAAACCCCCCUUCUCU	411	3836	UAACAAACCCCCCUUCUCU	411	3854	AGAGAAGGGGGGUUUGUUA	2163
rs3025843	3837	AACAAACCCCCCUUCUCUA	412	3837	AACAAACCCCCCUUCUCUA	412	3855	UAGAGAAGGGGGGUUUGUU	2164
rs3025843	3838	ACAAACCCCCCUUCUCUAA	413	3838	ACAAACCCCCCUUCUCUAA	413	3856	UUAGAGAAGGGGGGUUUGU	2165
rs3025843	3820	GCAGCCUUGCCUUCUCUAG	414	3820	GCAGCCUUGCCUUCUCUAG	414	3838	CUAGAGAAGGCAAGGCUGC	2166
rs3025843	3821	CAGCCUUGCCUUCUCUAGC	415	3821	CAGCCUUGCCUUCUCUAGC	415	3839	GCUAGAGAAGGCAAGGCUG	2167
rs3025843	3822	AGCCUUGCCUUCUCUAGCA	416	3822	AGCCUUGCCUUCUCUAGCA	416	3840	UGCUAGAGAAGGCAAGGCU	2168
rs3025843	3823	GCCUUGCCUUCUCUAGCAA	417	3823	GCCUUGCCUUCUCUAGCAA	417	3841	UUGCUAGAGAAGGCAAGGC	2169
rs3025843	3824	CCUUGCCUUCUCUAGCAAA	418	3824	CCUUGCCUUCUCUAGCAAA	418	3842	UUUGCUAGAGAAGGCAAGG	2170
rs3025843	3825	CUUGCCUUCUCUAGCAAAC	419	3825	CUUGCCUUCUCUAGCAAAC	419	3843	GUUUGCUAGAGAAGGCAAG	2171
rs3025843	3826	UUGCCUUCUCUAGCAAACC	420	3826	UUGCCUUCUCUAGCAAACC	420	3844	GGUUUGCUAGAGAAGGCAA	2172
rs3025843	3827	UGCCUUCUCUAGCAAACCC	421	3827	UGCCUUCUCUAGCAAACCC	421	3845	GGGUUUGCUAGAGAAGGCA	2173
rs3025843	3828	GCCUUCUCUAGCAAACCCC	422	3828	GCCUUCUCUAGCAAACCCC	422	3846	GGGGUUUGCUAGAGAAGGC	2174
rs3025843	3829	CCUUCUCUAGCAAACCCCC	423	3829	CCUUCUCUAGCAAACCCCC	423	3847	GGGGGUUUGCUAGAGAAGG	2175
rs3025843	3830	CUUCUCUAGCAAACCCCCC	424	3830	CUUCUCUAGCAAACCCCCC	424	3848	GGGGGGUUUGCUAGAGAAG	2176
rs3025843	3831	UUCUCUAGCAAACCCCCCU	425	3831	UUCUCUAGCAAACCCCCCU	425	3849	AGGGGGGUUUGCUAGAGAA	2177

rs3025843	3832	UCUCUAGCAAACCCCCCUU	426	3832	UCUCUAGCAAACCCCCCUU	426	3850	AAGGGGGGUUUGCUAGAGA	2178
rs3025843	3833	CUCUAGCAAACCCCCCUUC	427	3833	CUCUAGCAAACCCCCCUUC	427	3851	GAAGGGGGGUUUGCUAGAG	2179
rs3025843	3834	UCUAGCAAACCCCCCUUCU	428	3834	UCUAGCAAACCCCCCUUCU	428	3852	AGAAGGGGGGUUUGCUAGA	2180
rs3025843	3835	CUAGCAAACCCCCCUUCUC	429	3835	CUAGCAAACCCCCCUUCUC	429	3853	GAGAAGGGGGGUUUGCUAG	2181
rs3025843	3836	UAGCAAACCCCCCUUCUCU	430	3836	UAGCAAACCCCCCUUCUCU	430	3854	AGAGAAGGGGGGUUUGCUA	2182
rs3025843	3837	AGCAAACCCCCCUUCUCUA	431	3837	AGCAAACCCCCCUUCUCUA	431	3855	UAGAGAAGGGGGGUUUGCU	2183
rs3025843	3838	GCAAACCCCCCUUCUCUAA	432	3838	GCAAACCCCCCUUCUCUAA	432	3856	UUAGAGAAGGGGGGUUUGC	2184
rs4690074	4104	AAAGUUUGGAGGGUUUCUC	433	4104	AAAGUUUGGAGGGUUUCUC	433	4122	GAGAAACCCUCCAAACUUU	2185
rs4690074	4105	AAGUUUGGAGGGUUUCUCC	434	4105	AAGUUUGGAGGGUUUCUCC	434	4123	GGAGAAACCCUCCAAACUU	2186
rs4690074	4106	AGUUUGGAGGGUUUCUCCG	435	4106	AGUUUGGAGGGUUUCUCCG	435	4124	CGGAGAAACCCUCCAAACU	2187
rs4690074	4107	GUUUGGAGGGUUUCUCCGC	436	4107	GUUUGGAGGGUUUCUCCGC	436	4125	GCGGAGAAACCCUCCAAAC	2188
rs4690074	4108	UUUGGAGGGUUUCUCCGCU	437	4108	UUUGGAGGGUUUCUCCGCU	437	4126	AGCGGAGAAACCCUCCAAA	2189
rs4690074	4109	UUGGAGGGUUUCUCCGCUC	438	4109	UUGGAGGGUUUCUCCGCUC	438	4127	GAGCGGAGAAACCCUCCAA	2190
rs4690074	4110	UGGAGGGUUUCUCCGCUCA	439	4110	UGGAGGGUUUCUCCGCUCA	439	4128	UGAGCGGAGAAACCCUCCA	2191
rs4690074	4111	GGAGGGUUUCUCCGCUCAG	440	4111	GGAGGGUUUCUCCGCUCAG	440	4129	CUGAGCGGAGAAACCCUCC	2192
rs4690074	4112	GAGGGUUUCUCCGCUCAGC	441	4112	GAGGGUUUCUCCGCUCAGC	441	4130	GCUGAGCGGAGAAACCCUC	2193
rs4690074	4113	AGGGUUUCUCCGCUCAGCC	442	4113	AGGGUUUCUCCGCUCAGCC	442	4131	GGCUGAGCGGAGAAACCCU	2194
rs4690074	4114	GGGUUUCUCCGCUCAGCCU	443	4114	GGGUUUCUCCGCUCAGCCU	443	4132	AGGCUGAGCGGAGAAACCC	2195
rs4690074	4115	GGUUUCUCCGCUCAGCCUU	444	4115	GGUUUCUCCGCUCAGCCUU	444	4133	AAGGCUGAGCGGAGAAACC	2196
rs4690074	4116	GUUUCUCCGCUCAGCCUUG	445	4116	GUUUCUCCGCUCAGCCUUG	445	4134	CAAGGCUGAGCGGAGAAAC	2197
rs4690074	4117	UUUCUCCGCUCAGCCUUGG	446	4117	UUUCUCCGCUCAGCCUUGG	446	4135	CCAAGGCUGAGCGGAGAAA	2198
rs4690074	4118	UUCUCCGCUCAGCCUUGGA	447	4118	UUCUCCGCUCAGCCUUGGA	447	4136	UCCAAGGCUGAGCGGAGAA	2199
rs4690074	4119	UCUCCGCUCAGCCUUGGAU	448	4119	UCUCCGCUCAGCCUUGGAU	448	4137	AUCCAAGGCUGAGCGGAGA	2200
rs4690074	4120	CUCCGCUCAGCCUUGGAUG	449	4120	CUCCGCUCAGCCUUGGAUG	449	4138	CAUCCAAGGCUGAGCGGAG	2201
rs4690074	4121	UCCGCUCAGCCUUGGAUGU	450	4121	UCCGCUCAGCCUUGGAUGU	450	4139	ACAUCCAAGGCUGAGCGGA	2202
rs4690074	4122	CCGCUCAGCCUUGGAUGUU	451	4122	CCGCUCAGCCUUGGAUGUU	451	4140	AACAUCCAAGGCUGAGCGG	2203
rs4690074	4104	AAAGUUUGGAGGGUUUCUU	452	4104	AAAGUUUGGAGGGUUUCUU	452	4122	AAGAAACCCUCCAAACUUU	2204
rs4690074	4105	AAGUUUGGAGGGUUUCUUC	453	4105	AAGUUUGGAGGGUUUCUUC	453	4123	GAAGAAACCCUCCAAACUU	2205
rs4690074	4106	AGUUUGGAGGGUUUCUUCG	454	4106	AGUUUGGAGGGUUUCUUCG	454	4124	CGAAGAAACCCUCCAAACU	2206
rs4690074	4107	GUUUGGAGGGUUUCUUCGC	455	4107	GUUUGGAGGGUUUCUUCGC	455	4125	GCGAAGAAACCCUCCAAAC	2207
rs4690074	4108	UUUGGAGGGUUUCUUCGCU	456	4108	UUUGGAGGGUUUCUUCGCU	456	4126	AGCGAAGAAACCCUCCAAA	2208
rs4690074	4109	UUGGAGGGUUUCUUCGCUC	457	4109	UUGGAGGGUUUCUUCGCUC	457	4127	GAGCGAAGAAACCCUCCAA	2209
rs4690074	4110	UGGAGGGUUUCUUCGCUCA	458	4110	UGGAGGGUUUCUUCGCUCA	458	4128	UGAGCGAAGAAACCCUCCA	2210
rs4690074	4111	GGAGGGUUUCUUCGCUCAG	459	4111	GGAGGGUUUCUUCGCUCAG	459	4129	CUGAGCGAAGAAACCCUCC	2211
rs4690074	4112	GAGGGUUUCUUCGCUCAGC	460	4112	GAGGGUUUCUUCGCUCAGC	460	4130	GCUGAGCGAAGAAACCCUC	2212
rs4690074	4113	AGGGUUUCUUCGCUCAGCC	461	4113	AGGGUUUCUUCGCUCAGCC	461	4131	GGCUGAGCGAAGAAACCCU	2213
rs4690074	4114	GGGUUUCUUCGCUCAGCCU	462	4114	GGGUUUCUUCGCUCAGCCU	462	4132	AGGCUGAGCGAAGAAACCC	2214
rs4690074	4115	GGUUUCUUCGCUCAGCCUU	463	4115	GGUUUCUUCGCUCAGCCUU	463	4133	AAGGCUGAGCGAAGAAACC	2215
rs4690074	4116	GUUUCUUCGCUCAGCCUUG	464	4116	GUUUCUUCGCUCAGCCUUG	464	4134	CAAGGCUGAGCGAAGAAAC	2216

rs4690074	4117	UUUCUUCGCUCAGCCUUGG	465	4117	UUUCUUCGCUCAGCCUUGG	465	4135	CCAAGGCUGAGCGAAGAAA	2217
rs4690074	4118	UUCUUCGCUCAGCCUUGGA	466	4118	UUCUUCGCUCAGCCUUGGA	466	4136	UCCAAGGCUGAGCGAAGAA	2218
rs4690074	4119	UCUUCGCUCAGCCUUGGAU	467	4119	UCUUCGCUCAGCCUUGGAU	467	4137	AUCCAAGGCUGAGCGAAGA	2219
rs4690074	4120	CUUCGCUCAGCCUUGGAUG	468	4120	CUUCGCUCAGCCUUGGAUG	468	4138	CAUCCAAGGCUGAGCGAAG	2220
rs4690074	4121	UUCGCUCAGCCUUGGAUGU	469	4121	UUCGCUCAGCCUUGGAUGU	469	4139	ACAUCCAAGGCUGAGCGAA	2221
rs4690074	4122	UCGCUCAGCCUUGGAUGUU	470	4122	UCGCUCAGCCUUGGAUGUU	470	4140	AACAUCCAAGGCUGAGCGA	2222
rs3025837	4456	GUGCAGGCGGAGCAGGAGA	471	4456	GUGCAGGCGGAGCAGGAGA	471	4474	UCUCCUGCUCCGCCUGCAC	2223
rs3025837	4457	UGCAGGCGGAGCAGGAGAA	472	4457	UGCAGGCGGAGCAGGAGAA	472	4475	UUCUCCUGCUCCGCCUGCA	2224
rs3025837	4458	GCAGGCGGAGCAGGAGAAC	473	4458	GCAGGCGGAGCAGGAGAAC	473	4476	GUUCUCCUGCUCCGCCUGC	2225
rs3025837	4459	CAGGCGGAGCAGGAGAACG	474	4459	CAGGCGGAGCAGGAGAACG	474	4477	CGUUCUCCUGCUCCGCCUG	2226
rs3025837	4460	AGGCGGAGCAGGAGAACGA	475	4460	AGGCGGAGCAGGAGAACGA	475	4478	UCGUUCUCCUGCUCCGCCU	2227
rs3025837	4461	GGCGGAGCAGGAGAACGAC	476	4461	GGCGGAGCAGGAGAACGAC	476	4479	GUCGUUCUCCUGCUCCGCC	2228
rs3025837	4462	GCGGAGCAGGAGAACGACA	477	4462	GCGGAGCAGGAGAACGACA	477	4480	UGUCGUUCUCCUGCUCCGC	2229
rs3025837	4463	CGGAGCAGGAGAACGACAC	478	4463	CGGAGCAGGAGAACGACAC	478	4481	GUGUCGUUCUCCUGCUCCG	2230
rs3025837	4464	GGAGCAGGAGAACGACACC	479	4464	GGAGCAGGAGAACGACACC	479	4482	GGUGUCGUUCUCCUGCUCC	2231
rs3025837	4465	GAGCAGGAGAACGACACCU	480	4465	GAGCAGGAGAACGACACCU	480	4483	AGGUGUCGUUCUCCUGCUC	2232
rs3025837	4466	AGCAGGAGAACGACACCUC	481	4466	AGCAGGAGAACGACACCUC	481	4484	GAGGUGUCGUUCUCCUGCU	2233
rs3025837	4467	GCAGGAGAACGACACCUCG	482	4467	GCAGGAGAACGACACCUCG	482	4485	CGAGGUGUCGUUCUCCUGC	2234
rs3025837	4468	CAGGAGAACGACACCUCGG	483	4468	CAGGAGAACGACACCUCGG	483	4486	CCGAGGUGUCGUUCUCCUG	2235
rs3025837	4469	AGGAGAACGACACCUCGGG	484	4469	AGGAGAACGACACCUCGGG	484	4487	CCCGAGGUGUCGUUCUCCU	2236
rs3025837	4470	GGAGAACGACACCUCGGGA	485	4470	GGAGAACGACACCUCGGGA	485	4488	UCCCGAGGUGUCGUUCUCC	2237
rs3025837	4471	GAGAACGACACCUCGGGAU	486	4471	GAGAACGACACCUCGGGAU	486	4489	AUCCCGAGGUGUCGUUCUC	2238
rs3025837	4472	AGAACGACACCUCGGGAUG	487	4472	AGAACGACACCUCGGGAUG	487	4490	CAUCCCGAGGUGUCGUUCU	2239
rs3025837	4473	GAACGACACCUCGGGAUGG	488	4473	GAACGACACCUCGGGAUGG	488	4491	CCAUCCCGAGGUGUCGUUC	2240
rs3025837	4474	AACGACACCUCGGGAUGGU	489	4474	AACGACACCUCGGGAUGGU	489	4492	ACCAUCCCGAGGUGUCGUU	2241
rs3025837	4456	GUGCAGGCGGAGCAGGAGC	490	4456	GUGCAGGCGGAGCAGGAGC	490	4474	GCUCCUGCUCCGCCUGCAC	2242
rs3025837	4457	UGCAGGCGGAGCAGGAGCA	491	4457	UGCAGGCGGAGCAGGAGCA	491	4475	UGCUCCUGCUCCGCCUGCA	2243
rs3025837	4458	GCAGGCGGAGCAGGAGCAC	492	4458	GCAGGCGGAGCAGGAGCAC	492	4476	GUGCUCCUGCUCCGCCUGC	2244
rs3025837	4459	CAGGCGGAGCAGGAGCACG	493	4459	CAGGCGGAGCAGGAGCACG	493	4477	CGUGCUCCUGCUCCGCCUG	2245
rs3025837	4460	AGGCGGAGCAGGAGCACGA	494	4460	AGGCGGAGCAGGAGCACGA	494	4478	UCGUGCUCCUGCUCCGCCU	2246
rs3025837	4461	GGCGGAGCAGGAGCACGAC	495	4461	GGCGGAGCAGGAGCACGAC	495	4479	GUCGUGCUCCUGCUCCGCC	2247
rs3025837	4462	GCGGAGCAGGAGCACGACA	496	4462	GCGGAGCAGGAGCACGACA	496	4480	UGUCGUGCUCCUGCUCCGC	2248
rs3025837	4463	CGGAGCAGGAGCACGACAC	497	4463	CGGAGCAGGAGCACGACAC	497	4481	GUGUCGUGCUCCUGCUCCG	2249
rs3025837	4464	GGAGCAGGAGCACGACACC	498	4464	GGAGCAGGAGCACGACACC	498	4482	GGUGUCGUGCUCCUGCUCC	2250
rs3025837	4465	GAGCAGGAGCACGACACCU	499	4465	GAGCAGGAGCACGACACCU	499	4483	AGGUGUCGUGCUCCUGCUC	2251
rs3025837	4466	AGCAGGAGCACGACACCUC	500	4466	AGCAGGAGCACGACACCUC	500	4484	GAGGUGUCGUGCUCCUGCU	2252
rs3025837	4467	GCAGGAGCACGACACCUCG	501	4467	GCAGGAGCACGACACCUCG	501	4485	CGAGGUGUCGUGCUCCUGC	2253
rs3025837	4468	CAGGAGCACGACACCUCGG	502	4468	CAGGAGCACGACACCUCGG	502	4486	CCGAGGUGUCGUGCUCCUG	2254
rs3025837	4469	AGGAGCACGACACCUCGGG	503	4469	AGGAGCACGACACCUCGGG	503	4487	CCCGAGGUGUCGUGCUCCU	2255

rs3025837	4470	GGAGCACGACACCUCGGGA	504	4470	GGAGCACGACACCUCGGGA	504	4488	UCCCGAGGUGUCGUGCUCC	2256
rs3025837	4471	GAGCACGACACCUCGGGAU	505	4471	GAGCACGACACCUCGGGAU	505	4489	AUCCCGAGGUGUCGUGCUC	2257
rs3025837	4472	AGCACGACACCUCGGGAUG	506	4472	AGCACGACACCUCGGGAUG	506	4490	CAUCCCGAGGUGUCGUGCU	2258
rs3025837	4473	GCACGACACCUCGGGAUGG	507	4473	GCACGACACCUCGGGAUGG	507	4491	CCAUCCCGAGGUGUCGUGC	2259
rs3025837	4474	CACGACACCUCGGGAUGGU	508	4474	CACGACACCUCGGGAUGGU	508	4492	ACCAUCCCGAGGUGUCGUG	2260
rs363129	4967	UCUUUGUAUUAAGAGGAAC	509	4967	UCUUUGUAUUAAGAGGAAC	509	4985	GUUCCUCUUAAUACAAAGA	2261
rs363129	4968	CUUUGUAUUAAGAGGAACA	510	4968	CUUUGUAUUAAGAGGAACA	510	4986	UGUUCCUCUUAAUACAAAG	2262
rs363129	4969	UUUGUAUUAAGAGGAACAA	511	4969	UUUGUAUUAAGAGGAACAA	511	4987	UUGUUCCUCUUAAUACAAA	2263
rs363129	4970	UUGUAUUAAGAGGAACAAA	512	4970	UUGUAUUAAGAGGAACAAA	512	4988	UUUGUUCCUCUUAAUACAA	2264
rs363129	4971	UGUAUUAAGAGGAACAAAU	513	4971	UGUAUUAAGAGGAACAAAU	513	4989	AUUUGUUCCUCUUAAUACA	2265
rs363129	4972	GUAUUAAGAGGAACAAAUA	514	4972	GUAUUAAGAGGAACAAAUA	514	4990	UAUUUGUUCCUCUUAAUAC	2266
rs363129	4973	UAUUAAGAGGAACAAAUAA	515	4973	UAUUAAGAGGAACAAAUAA	515	4991	UUAUUUGUUCCUCUUAAUA	2267
rs363129	4974	AUUAAGAGGAACAAAUAAA	516	4974	AUUAAGAGGAACAAAUAAA	516	4992	UUUAUUUGUUCCUCUUAAU	2268
rs363129	4975	UUAAGAGGAACAAAUAAAG	517	4975	UUAAGAGGAACAAAUAAAG	517	4993	CUUUAUUUGUUCCUCUUAA	2269
rs363129	4976	UAAGAGGAACAAAUAAAGC	518	4976	UAAGAGGAACAAAUAAAGC	518	4994	GCUUUAUUUGUUCCUCUUA	2270
rs363129	4977	AAGAGGAACAAAUAAAGCU	519	4977	AAGAGGAACAAAUAAAGCU	519	4995	AGCUUUAUUUGUUCCUCUU	2271
rs363129	4978	AGAGGAACAAAUAAAGCUG	520	4978	AGAGGAACAAAUAAAGCUG	520	4996	CAGCUUUAUUUGUUCCUCU	2272
rs363129	4979	GAGGAACAAAUAAAGCUGA	521	4979	GAGGAACAAAUAAAGCUGA	521	4997	UCAGCUUUAUUUGUUCCUC	2273
rs363129	4980	AGGAACAAAUAAAGCUGAU	522	4980	AGGAACAAAUAAAGCUGAU	522	4998	AUCAGCUUUAUUUGUUCCU	2274
rs363129	4981	GGAACAAAUAAAGCUGAUG	523	4981	GGAACAAAUAAAGCUGAUG	523	4999	CAUCAGCUUUAUUUGUUCC	2275
rs363129	4982	GAACAAAUAAAGCUGAUGC	524	4982	GAACAAAUAAAGCUGAUGC	524	5000	GCAUCAGCUUUAUUUGUUC	2276
rs363129	4983	AACAAAUAAAGCUGAUGCA	525	4983	AACAAAUAAAGCUGAUGCA	525	5001	UGCAUCAGCUUUAUUUGUU	2277
rs363129	4984	ACAAAUAAAGCUGAUGCAG	526	4984	ACAAAUAAAGCUGAUGCAG	526	5002	CUGCAUCAGCUUUAUUUGU	2278
rs363129	4985	CAAAUAAAGCUGAUGCAGG	527	4985	CAAAUAAAGCUGAUGCAGG	527	5003	CCUGCAUCAGCUUUAUUUG	2279
rs363129	4967	UCUUUGUAUUAAGAGGAAU	528	4967	UCUUUGUAUUAAGAGGAAU	528	4985	AUUCCUCUUAAUACAAAGA	2280
rs363129	4968	CUUUGUAUUAAGAGGAAUA	529	4968	CUUUGUAUUAAGAGGAAUA	529	4986	UAUUCCUCUUAAUACAAAG	2281
rs363129	4969	UUUGUAUUAAGAGGAAUAA	530	4969	UUUGUAUUAAGAGGAAUAA	530	4987	UUAUUCCUCUUAAUACAAA	2282
rs363129	4970	UUGUAUUAAGAGGAAUAAA	531	4970	UUGUAUUAAGAGGAAUAAA	531	4988	UUUAUUCCUCUUAAUACAA	2283
rs363129	4971	UGUAUUAAGAGGAAUAAAU	532	4971	UGUAUUAAGAGGAAUAAAU	532	4989	AUUUAUUCCUCUUAAUACA	2284
rs363129	4972	GUAUUAAGAGGAAUAAAUA	533	4972	GUAUUAAGAGGAAUAAAUA	533	4990	UAUUUAUUCCUCUUAAUAC	2285
rs363129	4973	UAUUAAGAGGAAUAAAUAA	534	4973	UAUUAAGAGGAAUAAAUAA	534	4991	UUAUUUAUUCCUCUUAAUA	2286
rs363129	4974	AUUAAGAGGAAUAAAUAAA	535	4974	AUUAAGAGGAAUAAAUAAA	535	4992	UUUAUUUAUUCCUCUUAAU	2287
rs363129	4975	UUAAGAGGAAUAAAUAAAG	536	4975	UUAAGAGGAAUAAAUAAAG	536	4993	CUUUAUUUAUUCCUCUUAA	2288
rs363129	4976	UAAGAGGAAUAAAUAAAGC	537	4976	UAAGAGGAAUAAAUAAAGC	537	4994	GCUUUAUUUAUUCCUCUUA	2289
rs363129	4977	AAGAGGAAUAAAUAAAGCU	538	4977	AAGAGGAAUAAAUAAAGCU	538	4995	AGCUUUAUUUAUUCCUCUU	2290
rs363129	4978	AGAGGAAUAAAUAAAGCUG	539	4978	AGAGGAAUAAAUAAAGCUG	539	4996	CAGCUUUAUUUAUUCCUCU	2291
rs363129	4979	GAGGAAUAAAUAAAGCUGA	540	4979	GAGGAAUAAAUAAAGCUGA	540	4997	UCAGCUUUAUUUAUUCCUC	2292
rs363129	4980	AGGAAUAAAUAAAGCUGAU	541	4980	AGGAAUAAAUAAAGCUGAU	541	4998	AUCAGCUUUAUUUAUUCCU	2293
rs363129	4981	GGAAUAAAUAAAGCUGAUG	542	4981	GGAAUAAAUAAAGCUGAUG	542	4999	CAUCAGCUUUAUUUAUUCC	2294

rs363129	4982	GAAUAAAUAAAGCUGAUGC	543	4982	GAAUAAAUAAAGCUGAUGC	543	5000	GCAUCAGCUUUAUUUAUUC	2295
rs363129	4983	AAUAAAUAAAGCUGAUGCA	544	4983	AAUAAAUAAAGCUGAUGCA	544	5001	UGCAUCAGCUUUAUUUAUU	2296
rs363129	4984	AUAAAUAAAGCUGAUGCAG	545	4984	AUAAAUAAAGCUGAUGCAG	545	5002	CUGCAUCAGCUUUAUUUAU	2297
rs363129	4985	UAAAUAAAGCUGAUGCAGG	546	4985	UAAAUAAAGCUGAUGCAGG	546	5003	CCUGCAUCAGCUUUAUUUA	2298
rs363125	5462	UAAGAGAUGGGGACAGUAC	547	5462	UAAGAGAUGGGGACAGUAC	547	5480	GUACUGUCCCCAUCUCUUA	2299
rs363125	5463	AAGAGAUGGGGACAGUACU	548	5463	AAGAGAUGGGGACAGUACU	548	5481	AGUACUGUCCCCAUCUCUU	2300
rs363125	5464	AGAGAUGGGGACAGUACUU	549	5464	AGAGAUGGGGACAGUACUU	549	5482	AAGUACUGUCCCCAUCUCU	2301
rs363125	5465	GAGAUGGGGACAGUACUUC	550	5465	GAGAUGGGGACAGUACUUC	550	5483	GAAGUACUGUCCCCAUCUC	2302
rs363125	5466	AGAUGGGGACAGUACUUCA	551	5466	AGAUGGGGACAGUACUUCA	551	5484	UGAAGUACUGUCCCCAUCU	2303
rs363125	5467	GAUGGGGACAGUACUUCAA	552	5467	GAUGGGGACAGUACUUCAA	552	5485	UUGAAGUACUGUCCCCAUC	2304
rs363125	5468	AUGGGGACAGUACUUCAAC	553	5468	AUGGGGACAGUACUUCAAC	553	5486	GUUGAAGUACUGUCCCCAU	2305
rs363125	5469	UGGGGACAGUACUUCAACG	554	5469	UGGGGACAGUACUUCAACG	554	5487	CGUUGAAGUACUGUCCCCA	2306
rs363125	5470	GGGGACAGUACUUCAACGC	555	5470	GGGGACAGUACUUCAACGC	555	5488	GCGUUGAAGUACUGUCCCC	2307
rs363125	5471	GGGACAGUACUUCAACGCU	556	5471	GGGACAGUACUUCAACGCU	556	5489	AGCGUUGAAGUACUGUCCC	2308
rs363125	5472	GGACAGUACUUCAACGCUA	557	5472	GGACAGUACUUCAACGCUA	557	5490	UAGCGUUGAAGUACUGUCC	2309
rs363125	5473	GACAGUACUUCAACGCUAG	558	5473	GACAGUACUUCAACGCUAG	558	5491	CUAGCGUUGAAGUACUGUC	2310
rs363125	5474	ACAGUACUUCAACGCUAGA	559	5474	ACAGUACUUCAACGCUAGA	559	5492	UCUAGCGUUGAAGUACUGU	2311
rs363125	5475	CAGUACUUCAACGCUAGAA	560	5475	CAGUACUUCAACGCUAGAA	560	5493	UUCUAGCGUUGAAGUACUG	2312
rs363125	5476	AGUACUUCAACGCUAGAAG	561	5476	AGUACUUCAACGCUAGAAG	561	5494	CUUCUAGCGUUGAAGUACU	2313
rs363125	5477	GUACUUCAACGCUAGAAGA	562	5477	GUACUUCAACGCUAGAAGA	562	5495	UCUUCUAGCGUUGAAGUAC	2314
rs363125	5478	UACUUCAACGCUAGAAGAA	563	5478	UACUUCAACGCUAGAAGAA	563	5496	UUCUUCUAGCGUUGAAGUA	2315
rs363125	5479	ACUUCAACGCUAGAAGAAC	564	5479	ACUUCAACGCUAGAAGAAC	564	5497	GUUCUUCUAGCGUUGAAGU	2316
rs363125	5480	CUUCAACGCUAGAAGAACA	565	5480	CUUCAACGCUAGAAGAACA	565	5498	UGUUCUUCUAGCGUUGAAG	2317
rs363125	5462	UAAGAGAUGGGGACAGUAA	566	5462	UAAGAGAUGGGGACAGUAA	566	5480	UUACUGUCCCCAUCUCUUA	2318
rs363125	5463	AAGAGAUGGGGACAGUAAU	567	5463	AAGAGAUGGGGACAGUAAU	567	5481	AUUACUGUCCCCAUCUCUU	2319
rs363125	5464	AGAGAUGGGGACAGUAAUU	568	5464	AGAGAUGGGGACAGUAAUU	568	5482	AAUUACUGUCCCCAUCUCU	2320
rs363125	5465	GAGAUGGGGACAGUAAUUC	569	5465	GAGAUGGGGACAGUAAUUC	569	5483	GAAUUACUGUCCCCAUCUC	2321
rs363125	5466	AGAUGGGGACAGUAAUUCA	570	5466	AGAUGGGGACAGUAAUUCA	570	5484	UGAAUUACUGUCCCCAUCU	2322
rs363125	5467	GAUGGGGACAGUAAUUCAA	571	5467	GAUGGGGACAGUAAUUCAA	571	5485	UUGAAUUACUGUCCCCAUC	2323
rs363125	5468	AUGGGGACAGUAAUUCAAC	572	5468	AUGGGGACAGUAAUUCAAC	572	5486	GUUGAAUUACUGUCCCCAU	2324
rs363125	5469	UGGGGACAGUAAUUCAACG	573	5469	UGGGGACAGUAAUUCAACG	573	5487	CGUUGAAUUACUGUCCCCA	2325
rs363125	5470	GGGGACAGUAAUUCAACGC	574	5470	GGGGACAGUAAUUCAACGC	574	5488	GCGUUGAAUUACUGUCCCC	2326
rs363125	5471	GGGACAGUAAUUCAACGCU	575	5471	GGGACAGUAAUUCAACGCU	575	5489	AGCGUUGAAUUACUGUCCC	2327
rs363125	5472	GGACAGUAAUUCAACGCUA	576	5472	GGACAGUAAUUCAACGCUA	576	5490	UAGCGUUGAAUUACUGUCC	2328
rs363125	5473	GACAGUAAUUCAACGCUAG	577	5473	GACAGUAAUUCAACGCUAG	577	5491	CUAGCGUUGAAUUACUGUC	2329
rs363125	5474	ACAGUAAUUCAACGCUAGA	578	5474	ACAGUAAUUCAACGCUAGA	578	5492	UCUAGCGUUGAAUUACUGU	2330
rs363125	5475	CAGUAAUUCAACGCUAGAA	579	5475	CAGUAAUUCAACGCUAGAA	579	5493	UUCUAGCGUUGAAUUACUG	2331
rs363125	5476	AGUAAUUCAACGCUAGAAG	580	5476	AGUAAUUCAACGCUAGAAG	580	5494	CUUCUAGCGUUGAAUUACU	2332
rs363125	5477	GUAAUUCAACGCUAGAAGA	581	5477	GUAAUUCAACGCUAGAAGA	581	5495	UCUUCUAGCGUUGAAUUAC	2333

rs363125	5478	UAAUUCAACGCUAGAAGAA	582	5478	UAAUUCAACGCUAGAAGAA	582	5496	UUCUUCUAGCGUUGAAUUA	2334
rs363125	5479	AAUUCAACGCUAGAAGAAC	583	5479	AAUUCAACGCUAGAAGAAC	583	5497	GUUCUUCUAGCGUUGAAUU	2335
rs363125	5480	AUUCAACGCUAGAAGAACA	584	5480	AUUCAACGCUAGAAGAACA	584	5498	UGUUCUUCUAGCGUUGAAU	2336
rs4690077	6894	GCCCGAGCUGCCUGCAGAG	585	6894	GCCCGAGCUGCCUGCAGAG	585	6912	CUCUGCAGGCAGCUCGGGC	2337
rs4690077	6895	CCCGAGCUGCCUGCAGAGC	586	6895	CCCGAGCUGCCUGCAGAGC	586	6913	GCUCUGCAGGCAGCUCGGG	2338
rs4690077	6896	CCGAGCUGCCUGCAGAGCC	587	6896	CCGAGCUGCCUGCAGAGCC	587	6914	GGCUCUGCAGGCAGCUCGG	2339
rs4690077	6897	CGAGCUGCCUGCAGAGCCG	588	6897	CGAGCUGCCUGCAGAGCCG	588	6915	CGGCUCUGCAGGCAGCUCG	2340
rs4690077	6898	GAGCUGCCUGCAGAGCCGG	589	6898	GAGCUGCCUGCAGAGCCGG	589	6916	CCGGCUCUGCAGGCAGCUC	2341
rs4690077	6899	AGCUGCCUGCAGAGCCGGC	590	6899	AGCUGCCUGCAGAGCCGGC	590	6917	GCCGGCUCUGCAGGCAGCU	2342
rs4690077	6900	GCUGCCUGCAGAGCCGGCG	591	6900	GCUGCCUGCAGAGCCGGCG	591	6918	CGCCGGCUCUGCAGGCAGC	2343
rs4690077	6901	CUGCCUGCAGAGCCGGCGG	592	6901	CUGCCUGCAGAGCCGGCGG	592	6919	CCGCCGGCUCUGCAGGCAG	2344
rs4690077	6902	UGCCUGCAGAGCCGGCGGC	593	6902	UGCCUGCAGAGCCGGCGGC	593	6920	GCCGCCGGCUCUGCAGGCA	2345
rs4690077	6903	GCCUGCAGAGCCGGCGGCC	594	6903	GCCUGCAGAGCCGGCGGCC	594	6921	GGCCGCCGGCUCUGCAGGC	2346
rs4690077	6904	CCUGCAGAGCCGGCGGCCU	595	6904	CCUGCAGAGCCGGCGGCCU	595	6922	AGGCCGCCGGCUCUGCAGG	2347
rs4690077	6905	CUGCAGAGCCGGCGGCCUA	596	6905	CUGCAGAGCCGGCGGCCUA	596	6923	UAGGCCGCCGGCUCUGCAG	2348
rs4690077	6906	UGCAGAGCCGGCGGCCUAC	597	6906	UGCAGAGCCGGCGGCCUAC	597	6924	GUAGGCCGCCGGCUCUGCA	2349
rs4690077	6907	GCAGAGCCGGCGGCCUACU	598	6907	GCAGAGCCGGCGGCCUACU	598	6925	AGUAGGCCGCCGGCUCUGC	2350
rs4690077	6908	CAGAGCCGGCGGCCUACUG	599	6908	CAGAGCCGGCGGCCUACUG	599	6926	CAGUAGGCCGCCGGCUCUG	2351
rs4690077	6909	AGAGCCGGCGGCCUACUGG	600	6909	AGAGCCGGCGGCCUACUGG	600	6927	CCAGUAGGCCGCCGGCUCU	2352
rs4690077	6910	GAGCCGGCGGCCUACUGGA	601	6910	GAGCCGGCGGCCUACUGGA	601	6928	UCCAGUAGGCCGCCGGCUC	2353
rs4690077	6911	AGCCGGCGGCCUACUGGAG	602	6911	AGCCGGCGGCCUACUGGAG	602	6929	CUCCAGUAGGCCGCCGGCU	2354
rs4690077	6912	GCCGGCGGCCUACUGGAGC	603	6912	GCCGGCGGCCUACUGGAGC	603	6930	GCUCCAGUAGGCCGCCGGC	2355
rs4690077	6894	GCCCGAGCUGCCUGCAGAA	604	6894	GCCCGAGCUGCCUGCAGAA	604	6912	UUCUGCAGGCAGCUCGGGC	2356
rs4690077	6895	CCCGAGCUGCCUGCAGAAC	605	6895	CCCGAGCUGCCUGCAGAAC	605	6913	GUUCUGCAGGCAGCUCGGG	2357
rs4690077	6896	CCGAGCUGCCUGCAGAACC	606	6896	CCGAGCUGCCUGCAGAACC	606	6914	GGUUCUGCAGGCAGCUCGG	2358
rs4690077	6897	CGAGCUGCCUGCAGAACCG	607	6897	CGAGCUGCCUGCAGAACCG	607	6915	CGGUUCUGCAGGCAGCUCG	2359
rs4690077	6898	GAGCUGCCUGCAGAACCGG	608	6898	GAGCUGCCUGCAGAACCGG	608	6916	CCGGUUCUGCAGGCAGCUC	2360
rs4690077	6899	AGCUGCCUGCAGAACCGGC	609	6899	AGCUGCCUGCAGAACCGGC	609	6917	GCCGGUUCUGCAGGCAGCU	2361
rs4690077	6900	GCUGCCUGCAGAACCGGCG	610	6900	GCUGCCUGCAGAACCGGCG	610	6918	CGCCGGUUCUGCAGGCAGC	2362
rs4690077	6901	CUGCCUGCAGAACCGGCGG	611	6901	CUGCCUGCAGAACCGGCGG	611	6919	CCGCCGGUUCUGCAGGCAG	2363
rs4690077	6902	UGCCUGCAGAACCGGCGGC	612	6902	UGCCUGCAGAACCGGCGGC	612	6920	GCCGCCGGUUCUGCAGGCA	2364
rs4690077	6903	GCCUGCAGAACCGGCGGCC	613	6903	GCCUGCAGAACCGGCGGCC	613	6921	GGCCGCCGGUUCUGCAGGC	2365
rs4690077	6904	CCUGCAGAACCGGCGGCCU	614	6904	CCUGCAGAACCGGCGGCCU	614	6922	AGGCCGCCGGUUCUGCAGG	2366
rs4690077	6905	CUGCAGAACCGGCGGCCUA	615	6905	CUGCAGAACCGGCGGCCUA	615	6923	UAGGCCGCCGGUUCUGCAG	2367
rs4690077	6906	UGCAGAACCGGCGGCCUAC	616	6906	UGCAGAACCGGCGGCCUAC	616	6924	GUAGGCCGCCGGUUCUGCA	2368
rs4690077	6907	GCAGAACCGGCGGCCUACU	617	6907	GCAGAACCGGCGGCCUACU	617	6925	AGUAGGCCGCCGGUUCUGC	2369
rs4690077	6908	CAGAACCGGCGGCCUACUG	618	6908	CAGAACCGGCGGCCUACUG	618	6926	CAGUAGGCCGCCGGUUCUG	2370
rs4690077	6909	AGAACCGGCGGCCUACUGG	619	6909	AGAACCGGCGGCCUACUGG	619	6927	CCAGUAGGCCGCCGGUUCU	2371
rs4690077	6910	GAACCGGCGGCCUACUGGA	620	6910	GAACCGGCGGCCUACUGGA	620	6928	UCCAGUAGGCCGCCGGUUC	2372

rs4690077	6911	AACCGGCGGCCUACUGGAG	621	6911	AACCGGCGGCCUACUGGAG	621	6929	CUCCAGUAGGCCGCCGGUU	2373
rs4690077	6912	ACCGGCGGCCUACUGGAGC	622	6912	ACCGGCGGCCUACUGGAGC	622	6930	GCUCCAGUAGGCCGCCGGU	2374
rs362331	7228	CACGCCUGCUCCCUCAUCU	623	7228	CACGCCUGCUCCCUCAUCU	623	7246	AGAUGAGGGAGCAGGCGUG	2375
rs362331	7229	ACGCCUGCUCCCUCAUCUA	624	7229	ACGCCUGCUCCCUCAUCUA	624	7247	UAGAUGAGGGAGCAGGCGU	2376
rs362331	7230	CGCCUGCUCCCUCAUCUAC	625	7230	CGCCUGCUCCCUCAUCUAC	625	7248	GUAGAUGAGGGAGCAGGCG	2377
rs362331	7231	GCCUGCUCCCUCAUCUACU	626	7231	GCCUGCUCCCUCAUCUACU	626	7249	AGUAGAUGAGGGAGCAGGC	2378
rs362331	7232	CCUGCUCCCUCAUCUACUG	627	7232	CCUGCUCCCUCAUCUACUG	627	7250	CAGUAGAUGAGGGAGCAGG	2379
rs362331	7233	CUGCUCCCUCAUCUACUGU	628	7233	CUGCUCCCUCAUCUACUGU	628	7251	ACAGUAGAUGAGGGAGCAG	2380
rs362331	7234	UGCUCCCUCAUCUACUGUG	629	7234	UGCUCCCUCAUCUACUGUG	629	7252	CACAGUAGAUGAGGGAGCA	2381
rs362331	7235	GCUCCCUCAUCUACUGUGU	630	7235	GCUCCCUCAUCUACUGUGU	630	7253	ACACAGUAGAUGAGGGAGC	2382
rs362331	7236	CUCCCUCAUCUACUGUGUG	631	7236	CUCCCUCAUCUACUGUGUG	631	7254	CACACAGUAGAUGAGGGAG	2383
rs362331	7237	UCCCUCAUCUACUGUGUGC	632	7237	UCCCUCAUCUACUGUGUGC	632	7255	GCACACAGUAGAUGAGGGA	2384
rs362331	7238	CCCUCAUCUACUGUGUGCA	633	7238	CCCUCAUCUACUGUGUGCA	633	7256	UGCACACAGUAGAUGAGGG	2385
rs362331	7239	CCUCAUCUACUGUGUGCAC	634	7239	CCUCAUCUACUGUGUGCAC	634	7257	GUGCACACAGUAGAUGAGG	2386
rs362331	7240	CUCAUCUACUGUGUGCACU	635	7240	CUCAUCUACUGUGUGCACU	635	7258	AGUGCACACAGUAGAUGAG	2387
rs362331	7241	UCAUCUACUGUGUGCACUU	636	7241	UCAUCUACUGUGUGCACUU	636	7259	AAGUGCACACAGUAGAUGA	2388
rs362331	7242	CAUCUACUGUGUGCACUUC	637	7242	CAUCUACUGUGUGCACUUC	637	7260	GAAGUGCACACAGUAGAUG	2389
rs362331	7243	AUCUACUGUGUGCACUUCA	638	7243	AUCUACUGUGUGCACUUCA	638	7261	UGAAGUGCACACAGUAGAU	2390
rs362331	7244	UCUACUGUGUGCACUUCAU	639	7244	UCUACUGUGUGCACUUCAU	639	7262	AUGAAGUGCACACAGUAGA	2391
rs362331	7245	CUACUGUGUGCACUUCAUC	640	7245	CUACUGUGUGCACUUCAUC	640	7263	GAUGAAGUGCACACAGUAG	2392
rs362331	7246	UACUGUGUGCACUUCAUCC	641	7246	UACUGUGUGCACUUCAUCC	641	7264	GGAUGAAGUGCACACAGUA	2393
rs362331	7228	CACGCCUGCUCCCUCAUCC	642	7228	CACGCCUGCUCCCUCAUCC	642	7246	GGAUGAGGGAGCAGGCGUG	2394
rs362331	7229	ACGCCUGCUCCCUCAUCCA	643	7229	ACGCCUGCUCCCUCAUCCA	643	7247	UGGAUGAGGGAGCAGGCGU	2395
rs362331	7230	CGCCUGCUCCCUCAUCCAC	644	7230	CGCCUGCUCCCUCAUCCAC	644	7248	GUGGAUGAGGGAGCAGGCG	2396
rs362331	7231	GCCUGCUCCCUCAUCCACU	645	7231	GCCUGCUCCCUCAUCCACU	645	7249	AGUGGAUGAGGGAGCAGGC	2397
rs362331	7232	CCUGCUCCCUCAUCCACUG	646	7232	CCUGCUCCCUCAUCCACUG	646	7250	CAGUGGAUGAGGGAGCAGG	2398
rs362331	7233	CUGCUCCCUCAUCCACUGU	647	7233	CUGCUCCCUCAUCCACUGU	647	7251	ACAGUGGAUGAGGGAGCAG	2399
rs362331	7234	UGCUCCCUCAUCCACUGUG	648	7234	UGCUCCCUCAUCCACUGUG	648	7252	CACAGUGGAUGAGGGAGCA	2400
rs362331	7235	GCUCCCUCAUCCACUGUGU	649	7235	GCUCCCUCAUCCACUGUGU	649	7253	ACACAGUGGAUGAGGGAGC	2401
rs362331	7236	CUCCCUCAUCCACUGUGUG	650	7236	CUCCCUCAUCCACUGUGUG	650	7254	CACACAGUGGAUGAGGGAG	2402
rs362331	7237	UCCCUCAUCCACUGUGUGC	651	7237	UCCCUCAUCCACUGUGUGC	651	7255	GCACACAGUGGAUGAGGGA	2403
rs362331	7238	CCCUCAUCCACUGUGUGCA	652	7238	CCCUCAUCCACUGUGUGCA	652	7256	UGCACACAGUGGAUGAGGG	2404
rs362331	7239	CCUCAUCCACUGUGUGCAC	653	7239	CCUCAUCCACUGUGUGCAC	653	7257	GUGCACACAGUGGAUGAGG	2405
rs362331	7240	CUCAUCCACUGUGUGCACU	654	7240	CUCAUCCACUGUGUGCACU	654	7258	AGUGCACACAGUGGAUGAG	2406
rs362331	7241	UCAUCCACUGUGUGCACUU	655	7241	UCAUCCACUGUGUGCACUU	655	7259	AAGUGCACACAGUGGAUGA	2407
rs362331	7242	CAUCCACUGUGUGCACUUC	656	7242	CAUCCACUGUGUGCACUUC	656	7260	GAAGUGCACACAGUGGAUG	2408
rs362331	7243	AUCCACUGUGUGCACUUCA	657	7243	AUCCACUGUGUGCACUUCA	657	7261	UGAAGUGCACACAGUGGAU	2409
rs362331	7244	UCCACUGUGUGCACUUCAU	658	7244	UCCACUGUGUGCACUUCAU	658	7262	AUGAAGUGCACACAGUGGA	2410
rs362331	7245	CCACUGUGUGCACUUCAUC	659	7245	CCACUGUGUGCACUUCAUC	659	7263	GAUGAAGUGCACACAGUGG	2411

rs362331	7246	CACUGUGUGCACUUCAUCC	660	7246	CACUGUGUGCACUUCAUCC	660	7264	GGAUGAAGUGCACACAGUG	2412
rs3025818	7365	AAACACACAGAAUCCUAAG	661	7365	AAACACACAGAAUCCUAAG	661	7383	CUUAGGAUUCUGUGUGUUU	2413
rs3025818	7366	AACACACAGAAUCCUAAGU	662	7366	AACACACAGAAUCCUAAGU	662	7384	ACUUAGGAUUCUGUGUGUU	2414
rs3025818	7367	ACACACAGAAUCCUAAGUA	663	7367	ACACACAGAAUCCUAAGUA	663	7385	UACUUAGGAUUCUGUGUGU	2415
rs3025818	7368	CACACAGAAUCCUAAGUAU	664	7368	CACACAGAAUCCUAAGUAU	664	7386	AUACUUAGGAUUCUGUGUG	2416
rs3025818	7369	ACACAGAAUCCUAAGUAUA	665	7369	ACACAGAAUCCUAAGUAUA	665	7387	UAUACUUAGGAUUCUGUGU	2417
rs3025818	7370	CACAGAAUCCUAAGUAUAU	666	7370	CACAGAAUCCUAAGUAUAU	666	7388	AUAUACUUAGGAUUCUGUG	2418
rs3025818	7371	ACAGAAUCCUAAGUAUAUC	667	7371	ACAGAAUCCUAAGUAUAUC	667	7389	GAUAUACUUAGGAUUCUGU	2419
rs3025818	7372	CAGAAUCCUAAGUAUAUCA	668	7372	CAGAAUCCUAAGUAUAUCA	668	7390	UGAUAUACUUAGGAUUCUG	2420
rs3025818	7373	AGAAUCCUAAGUAUAUCAC	669	7373	AGAAUCCUAAGUAUAUCAC	669	7391	GUGAUAUACUUAGGAUUCU	2421
rs3025818	7374	GAAUCCUAAGUAUAUCACU	670	7374	GAAUCCUAAGUAUAUCACU	670	7392	AGUGAUAUACUUAGGAUUC	2422
rs3025818	7375	AAUCCUAAGUAUAUCACUG	671	7375	AAUCCUAAGUAUAUCACUG	671	7393	CAGUGAUAUACUUAGGAUU	2423
rs3025818	7376	AUCCUAAGUAUAUCACUGC	672	7376	AUCCUAAGUAUAUCACUGC	672	7394	GCAGUGAUAUACUUAGGAU	2424
rs3025818	7377	UCCUAAGUAUAUCACUGCA	673	7377	UCCUAAGUAUAUCACUGCA	673	7395	UGCAGUGAUAUACUUAGGA	2425
rs3025818	7378	CCUAAGUAUAUCACUGCAG	674	7378	CCUAAGUAUAUCACUGCAG	674	7396	CUGCAGUGAUAUACUUAGG	2426
rs3025818	7379	CUAAGUAUAUCACUGCAGC	675	7379	CUAAGUAUAUCACUGCAGC	675	7397	GCUGCAGUGAUAUACUUAG	2427
rs3025818	7380	UAAGUAUAUCACUGCAGCC	676	7380	UAAGUAUAUCACUGCAGCC	676	7398	GGCUGCAGUGAUAUACUUA	2428
rs3025818	7381	AAGUAUAUCACUGCAGCCU	677	7381	AAGUAUAUCACUGCAGCCU	677	7399	AGGCUGCAGUGAUAUACUU	2429
rs3025818	7382	AGUAUAUCACUGCAGCCUG	678	7382	AGUAUAUCACUGCAGCCUG	678	7400	CAGGCUGCAGUGAUAUACU	2430
rs3025818	7383	GUAUAUCACUGCAGCCUGU	679	7383	GUAUAUCACUGCAGCCUGU	679	7401	ACAGGCUGCAGUGAUAUAC	2431
rs3025818	7365	AAACACACAGAAUCCUAAA	680	7365	AAACACACAGAAUCCUAAA	680	7383	UUUAGGAUUCUGUGUGUUU	2432
rs3025818	7366	AACACACAGAAUCCUAAAU	681	7366	AACACACAGAAUCCUAAAU	681	7384	AUUUAGGAUUCUGUGUGUU	2433
rs3025818	7367	ACACACAGAAUCCUAAAUA	682	7367	ACACACAGAAUCCUAAAUA	682	7385	UAUUUAGGAUUCUGUGUGU	2434
rs3025818	7368	CACACAGAAUCCUAAAUAU	683	7368	CACACAGAAUCCUAAAUAU	683	7386	AUAUUUAGGAUUCUGUGUG	2435
rs3025818	7369	ACACAGAAUCCUAAAUAUA	684	7369	ACACAGAAUCCUAAAUAUA	684	7387	UAUAUUUAGGAUUCUGUGU	2436
rs3025818	7370	CACAGAAUCCUAAAUAUAU	685	7370	CACAGAAUCCUAAAUAUAU	685	7388	AUAUAUUUAGGAUUCUGUG	2437
rs3025818	7371	ACAGAAUCCUAAAUAUAUC	686	7371	ACAGAAUCCUAAAUAUAUC	686	7389	GAUAUAUUUAGGAUUCUGU	2438
rs3025818	7372	CAGAAUCCUAAAUAUAUCA	687	7372	CAGAAUCCUAAAUAUAUCA	687	7390	UGAUAUAUUUAGGAUUCUG	2439
rs3025818	7373	AGAAUCCUAAAUAUAUCAC	688	7373	AGAAUCCUAAAUAUAUCAC	688	7391	GUGAUAUAUUUAGGAUUCU	2440
rs3025818	7374	GAAUCCUAAAUAUAUCACU	689	7374	GAAUCCUAAAUAUAUCACU	689	7392	AGUGAUAUAUUUAGGAUUC	2441
rs3025818	7375	AAUCCUAAAUAUAUCACUG	690	7375	AAUCCUAAAUAUAUCACUG	690	7393	CAGUGAUAUAUUUAGGAUU	2442
rs3025818	7376	AUCCUAAAUAUAUCACUGC	691	7376	AUCCUAAAUAUAUCACUGC	691	7394	GCAGUGAUAUAUUUAGGAU	2443
rs3025818	7377	UCCUAAAUAUAUCACUGCA	692	7377	UCCUAAAUAUAUCACUGCA	692	7395	UGCAGUGAUAUAUUUAGGA	2444
rs3025818	7378	CCUAAAUAUAUCACUGCAG	693	7378	CCUAAAUAUAUCACUGCAG	693	7396	CUGCAGUGAUAUAUUUAGG	2445
rs3025818	7379	CUAAAUAUAUCACUGCAGC	694	7379	CUAAAUAUAUCACUGCAGC	694	7397	GCUGCAGUGAUAUAUUUAG	2446
rs3025818	7380	UAAAUAUAUCACUGCAGCC	695	7380	UAAAUAUAUCACUGCAGCC	695	7398	GGCUGCAGUGAUAUAUUUA	2447
rs3025818	7381	AAAUAUAUCACUGCAGCCU	696	7381	AAAUAUAUCACUGCAGCCU	696	7399	AGGCUGCAGUGAUAUAUUU	2448
rs3025818	7382	AAUAUAUCACUGCAGCCUG	697	7382	AAUAUAUCACUGCAGCCUG	697	7400	CAGGCUGCAGUGAUAUAUU	2449
rs3025818	7383	AUAUAUCACUGCAGCCUGU	698	7383	AUAUAUCACUGCAGCCUGU	698	7401	ACAGGCUGCAGUGAUAUAU	2450

rs2857790	7479	GUUUCUCACGCCAUUGCUC	699	7479	GUUUCUCACGCCAUUGCUC	699	7497	GAGCAAUGGCGUGAGAAAC	2451
rs2857790	7480	UUUCUCACGCCAUUGCUCA	700	7480	UUUCUCACGCCAUUGCUCA	700	7498	UGAGCAAUGGCGUGAGAAA	2452
rs2857790	7481	UUCUCACGCCAUUGCUCAG	701	7481	UUCUCACGCCAUUGCUCAG	701	7499	CUGAGCAAUGGCGUGAGAA	2453
rs2857790	7482	UCUCACGCCAUUGCUCAGG	702	7482	UCUCACGCCAUUGCUCAGG	702	7500	CCUGAGCAAUGGCGUGAGA	2454
rs2857790	7483	CUCACGCCAUUGCUCAGGA	703	7483	CUCACGCCAUUGCUCAGGA	703	7501	UCCUGAGCAAUGGCGUGAG	2455
rs2857790	7484	UCACGCCAUUGCUCAGGAA	704	7484	UCACGCCAUUGCUCAGGAA	704	7502	UUCCUGAGCAAUGGCGUGA	2456
rs2857790	7485	CACGCCAUUGCUCAGGAAC	705	7485	CACGCCAUUGCUCAGGAAC	705	7503	GUUCCUGAGCAAUGGCGUG	2457
rs2857790	7486	ACGCCAUUGCUCAGGAACA	706	7486	ACGCCAUUGCUCAGGAACA	706	7504	UGUUCCUGAGCAAUGGCGU	2458
rs2857790	7487	CGCCAUUGCUCAGGAACAU	707	7487	CGCCAUUGCUCAGGAACAU	707	7505	AUGUUCCUGAGCAAUGGCG	2459
rs2857790	7488	GCCAUUGCUCAGGAACAUC	708	7488	GCCAUUGCUCAGGAACAUC	708	7506	GAUGUUCCUGAGCAAUGGC	2460
rs2857790	7489	CCAUUGCUCAGGAACAUCA	709	7489	CCAUUGCUCAGGAACAUCA	709	7507	UGAUGUUCCUGAGCAAUGG	2461
rs2857790	7490	CAUUGCUCAGGAACAUCAU	710	7490	CAUUGCUCAGGAACAUCAU	710	7508	AUGAUGUUCCUGAGCAAUG	2462
rs2857790	7491	AUUGCUCAGGAACAUCAUC	711	7491	AUUGCUCAGGAACAUCAUC	711	7509	GAUGAUGUUCCUGAGCAAU	2463
rs2857790	7492	UUGCUCAGGAACAUCAUCA	712	7492	UUGCUCAGGAACAUCAUCA	712	7510	UGAUGAUGUUCCUGAGCAA	2464
rs2857790	7493	UGCUCAGGAACAUCAUCAU	713	7493	UGCUCAGGAACAUCAUCAU	713	7511	AUGAUGAUGUUCCUGAGCA	2465
rs2857790	7494	GCUCAGGAACAUCAUCAUC	714	7494	GCUCAGGAACAUCAUCAUC	714	7512	GAUGAUGAUGUUCCUGAGC	2466
rs2857790	7495	CUCAGGAACAUCAUCAUCA	715	7495	CUCAGGAACAUCAUCAUCA	715	7513	UGAUGAUGAUGUUCCUGAG	2467
rs2857790	7496	UCAGGAACAUCAUCAUCAG	716	7496	UCAGGAACAUCAUCAUCAG	716	7514	CUGAUGAUGAUGUUCCUGA	2468
rs2857790	7497	CAGGAACAUCAUCAUCAGC	717	7497	CAGGAACAUCAUCAUCAGC	717	7515	GCUGAUGAUGAUGUUCCUG	2469
rs2857790	7479	GUUUCUCACGCCAUUGCUA	718	7479	GUUUCUCACGCCAUUGCUA	718	7497	UAGCAAUGGCGUGAGAAAC	2470
rs2857790	7480	UUUCUCACGCCAUUGCUAA	719	7480	UUUCUCACGCCAUUGCUAA	719	7498	UUAGCAAUGGCGUGAGAAA	2471
rs2857790	7481	UUCUCACGCCAUUGCUAAG	720	7481	UUCUCACGCCAUUGCUAAG	720	7499	CUUAGCAAUGGCGUGAGAA	2472
rs2857790	7482	UCUCACGCCAUUGCUAAGG	721	7482	UCUCACGCCAUUGCUAAGG	721	7500	CCUUAGCAAUGGCGUGAGA	2473
rs2857790	7483	CUCACGCCAUUGCUAAGGA	722	7483	CUCACGCCAUUGCUAAGGA	722	7501	UCCUUAGCAAUGGCGUGAG	2474
rs2857790	7484	UCACGCCAUUGCUAAGGAA	723	7484	UCACGCCAUUGCUAAGGAA	723	7502	UUCCUUAGCAAUGGCGUGA	2475
rs2857790	7485	CACGCCAUUGCUAAGGAAC	724	7485	CACGCCAUUGCUAAGGAAC	724	7503	GUUCCUUAGCAAUGGCGUG	2476
rs2857790	7486	ACGCCAUUGCUAAGGAACA	725	7486	ACGCCAUUGCUAAGGAACA	725	7504	UGUUCCUUAGCAAUGGCGU	2477
rs2857790	7487	CGCCAUUGCUAAGGAACAU	726	7487	CGCCAUUGCUAAGGAACAU	726	7505	AUGUUCCUUAGCAAUGGCG	2478
rs2857790	7488	GCCAUUGCUAAGGAACAUC	727	7488	GCCAUUGCUAAGGAACAUC	727	7506	GAUGUUCCUUAGCAAUGGC	2479
rs2857790	7489	CCAUUGCUAAGGAACAUCA	728	7489	CCAUUGCUAAGGAACAUCA	728	7507	UGAUGUUCCUUAGCAAUGG	2480
rs2857790	7490	CAUUGCUAAGGAACAUCAU	729	7490	CAUUGCUAAGGAACAUCAU	729	7508	AUGAUGUUCCUUAGCAAUG	2481
rs2857790	7491	AUUGCUAAGGAACAUCAUC	730	7491	AUUGCUAAGGAACAUCAUC	730	7509	GAUGAUGUUCCUUAGCAAU	2482
rs2857790	7492	UUGCUAAGGAACAUCAUCA	731	7492	UUGCUAAGGAACAUCAUCA	731	7510	UGAUGAUGUUCCUUAGCAA	2483
rs2857790	7493	UGCUAAGGAACAUCAUCAU	732	7493	UGCUAAGGAACAUCAUCAU	732	7511	AUGAUGAUGUUCCUUAGCA	2484
rs2857790	7494	GCUAAGGAACAUCAUCAUC	733	7494	GCUAAGGAACAUCAUCAUC	733	7512	GAUGAUGAUGUUCCUUAGC	2485
rs2857790	7495	CUAAGGAACAUCAUCAUCA	734	7495	CUAAGGAACAUCAUCAUCA	734	7513	UGAUGAUGAUGUUCCUUAG	2486
rs2857790	7496	UAAGGAACAUCAUCAUCAG	735	7496	UAAGGAACAUCAUCAUCAG	735	7514	CUGAUGAUGAUGUUCCUUA	2487
rs2857790	7497	AAGGAACAUCAUCAUCAGC	736	7497	AAGGAACAUCAUCAUCAGC	736	7515	GCUGAUGAUGAUGUUCCUU	2488
rs362321	7665	GUUCAUCUACCGCAUCAAC	737	7665	GUUCAUCUACCGCAUCAAC	737	7683	GUUGAUGCGGUAGAUGAAC	2489

rs362321	7666	UUCAUCUACCGCAUCAACA	738	7666	UUCAUCUACCGCAUCAACA	738	7684	UGUUGAUGCGGUAGAUGAA	2490
rs362321	7667	UCAUCUACCGCAUCAACAC	739	7667	UCAUCUACCGCAUCAACAC	739	7685	GUGUUGAUGCGGUAGAUGA	2491
rs362321	7668	CAUCUACCGCAUCAACACA	740	7668	CAUCUACCGCAUCAACACA	740	7686	UGUGUUGAUGCGGUAGAUG	2492
rs362321	7669	AUCUACCGCAUCAACACAC	741	7669	AUCUACCGCAUCAACACAC	741	7687	GUGUGUUGAUGCGGUAGAU	2493
rs362321	7670	UCUACCGCAUCAACACACU	742	7670	UCUACCGCAUCAACACACU	742	7688	AGUGUGUUGAUGCGGUAGA	2494
rs362321	7671	CUACCGCAUCAACACACUA	743	7671	CUACCGCAUCAACACACUA	743	7689	UAGUGUGUUGAUGCGGUAG	2495
rs362321	7672	UACCGCAUCAACACACUAG	744	7672	UACCGCAUCAACACACUAG	744	7690	CUAGUGUGUUGAUGCGGUA	2496
rs362321	7673	ACCGCAUCAACACACUAGG	745	7673	ACCGCAUCAACACACUAGG	745	7691	CCUAGUGUGUUGAUGCGGU	2497
rs362321	7674	CCGCAUCAACACACUAGGC	746	7674	CCGCAUCAACACACUAGGC	746	7692	GCCUAGUGUGUUGAUGCGG	2498
rs362321	7675	CGCAUCAACACACUAGGCU	747	7675	CGCAUCAACACACUAGGCU	747	7693	AGCCUAGUGUGUUGAUGCG	2499
rs362321	7676	GCAUCAACACACUAGGCUG	748	7676	GCAUCAACACACUAGGCUG	748	7694	CAGCCUAGUGUGUUGAUGC	2500
rs362321	7677	CAUCAACACACUAGGCUGG	749	7677	CAUCAACACACUAGGCUGG	749	7695	CCAGCCUAGUGUGUUGAUG	2501
rs362321	7678	AUCAACACACUAGGCUGGA	750	7678	AUCAACACACUAGGCUGGA	750	7696	UCCAGCCUAGUGUGUUGAU	2502
rs362321	7679	UCAACACACUAGGCUGGAC	751	7679	UCAACACACUAGGCUGGAC	751	7697	GUCCAGCCUAGUGUGUUGA	2503
rs362321	7680	CAACACACUAGGCUGGACC	752	7680	CAACACACUAGGCUGGACC	752	7698	GGUCCAGCCUAGUGUGUUG	2504
rs362321	7681	AACACACUAGGCUGGACCA	753	7681	AACACACUAGGCUGGACCA	753	7699	UGGUCCAGCCUAGUGUGUU	2505
rs362321	7682	ACACACUAGGCUGGACCAG	754	7682	ACACACUAGGCUGGACCAG	754	7700	CUGGUCCAGCCUAGUGUGU	2506
rs362321	7683	CACACUAGGCUGGACCAGU	755	7683	CACACUAGGCUGGACCAGU	755	7701	ACUGGUCCAGCCUAGUGUG	2507
rs362321	7665	GUUCAUCUACCGCAUCAAU	756	7665	GUUCAUCUACCGCAUCAAU	756	7683	AUUGAUGCGGUAGAUGAAC	2508
rs362321	7666	UUCAUCUACCGCAUCAAUA	757	7666	UUCAUCUACCGCAUCAAUA	757	7684	UAUUGAUGCGGUAGAUGAA	2509
rs362321	7667	UCAUCUACCGCAUCAAUAC	758	7667	UCAUCUACCGCAUCAAUAC	758	7685	GUAUUGAUGCGGUAGAUGA	2510
rs362321	7668	CAUCUACCGCAUCAAUACA	759	7668	CAUCUACCGCAUCAAUACA	759	7686	UGUAUUGAUGCGGUAGAUG	2511
rs362321	7669	AUCUACCGCAUCAAUACAC	760	7669	AUCUACCGCAUCAAUACAC	760	7687	GUGUAUUGAUGCGGUAGAU	2512
rs362321	7670	UCUACCGCAUCAAUACACU	761	7670	UCUACCGCAUCAAUACACU	761	7688	AGUGUAUUGAUGCGGUAGA	2513
rs362321	7671	CUACCGCAUCAAUACACUA	762	7671	CUACCGCAUCAAUACACUA	762	7689	UAGUGUAUUGAUGCGGUAG	2514
rs362321	7672	UACCGCAUCAAUACACUAG	763	7672	UACCGCAUCAAUACACUAG	763	7690	CUAGUGUAUUGAUGCGGUA	2515
rs362321	7673	ACCGCAUCAAUACACUAGG	764	7673	ACCGCAUCAAUACACUAGG	764	7691	CCUAGUGUAUUGAUGCGGU	2516
rs362321	7674	CCGCAUCAAUACACUAGGC	765	7674	CCGCAUCAAUACACUAGGC	765	7692	GCCUAGUGUAUUGAUGCGG	2517
rs362321	7675	CGCAUCAAUACACUAGGCU	766	7675	CGCAUCAAUACACUAGGCU	766	7693	AGCCUAGUGUAUUGAUGCG	2518
rs362321	7676	GCAUCAAUACACUAGGCUG	767	7676	GCAUCAAUACACUAGGCUG	767	7694	CAGCCUAGUGUAUUGAUGC	2519
rs362321	7677	CAUCAAUACACUAGGCUGG	768	7677	CAUCAAUACACUAGGCUGG	768	7695	CCAGCCUAGUGUAUUGAUG	2520
rs362321	7678	AUCAAUACACUAGGCUGGA	769	7678	AUCAAUACACUAGGCUGGA	769	7696	UCCAGCCUAGUGUAUUGAU	2521
rs362321	7679	UCAAUACACUAGGCUGGAC	770	7679	UCAAUACACUAGGCUGGAC	770	7697	GUCCAGCCUAGUGUAUUGA	2522
rs362321	7680	CAAUACACUAGGCUGGACC	771	7680	CAAUACACUAGGCUGGACC	771	7698	GGUCCAGCCUAGUGUAUUG	2523
rs362321	7681	AAUACACUAGGCUGGACCA	772	7681	AAUACACUAGGCUGGACCA	772	7699	UGGUCCAGCCUAGUGUAUU	2524
rs362321	7682	AUACACUAGGCUGGACCAG	773	7682	AUACACUAGGCUGGACCAG	773	7700	CUGGUCCAGCCUAGUGUAU	2525
rs362321	7683	UACACUAGGCUGGACCAGU	774	7683	UACACUAGGCUGGACCAGU	774	7701	ACUGGUCCAGCCUAGUGUA	2526
rs3025816	7735	CUUGGUGUCCUGGUGACGC	775	7735	CUUGGUGUCCUGGUGACGC	775	7753	GCGUCACCAGGACACCAAG	2527
rs3025816	7736	UUGGUGUCCUGGUGACGCA	776	7736	UUGGUGUCCUGGUGACGCA	776	7754	UGCGUCACCAGGACACCAA	2528

rs3025816	7737	UGGUGUCCUGGUGACGCAG	777	7737	UGGUGUCCUGGUGACGCAG	777	7755	CUGCGUCACCAGGACACCA	2529
rs3025816	7738	GGUGUCCUGGUGACGCAGC	778	7738	GGUGUCCUGGUGACGCAGC	778	7756	GCUGCGUCACCAGGACACC	2530
rs3025816	7739	GUGUCCUGGUGACGCAGCC	779	7739	GUGUCCUGGUGACGCAGCC	779	7757	GGCUGCGUCACCAGGACAC	2531
rs3025816	7740	UGUCCUGGUGACGCAGCCC	780	7740	UGUCCUGGUGACGCAGCCC	780	7758	GGGCUGCGUCACCAGGACA	2532
rs3025816	7741	GUCCUGGUGACGCAGCCCC	781	7741	GUCCUGGUGACGCAGCCCC	781	7759	GGGGCUGCGUCACCAGGAC	2533
rs3025816	7742	UCCUGGUGACGCAGCCCCU	782	7742	UCCUGGUGACGCAGCCCCU	782	7760	AGGGGCUGCGUCACCAGGA	2534
rs3025816	7743	CCUGGUGACGCAGCCCCUC	783	7743	CCUGGUGACGCAGCCCCUC	783	7761	GAGGGGCUGCGUCACCAGG	2535
rs3025816	7744	CUGGUGACGCAGCCCCUCG	784	7744	CUGGUGACGCAGCCCCUCG	784	7762	CGAGGGGCUGCGUCACCAG	2536
rs3025816	7745	UGGUGACGCAGCCCCUCGU	785	7745	UGGUGACGCAGCCCCUCGU	785	7763	ACGAGGGGCUGCGUCACCA	2537
rs3025816	7746	GGUGACGCAGCCCCUCGUG	786	7746	GGUGACGCAGCCCCUCGUG	786	7764	CACGAGGGGCUGCGUCACC	2538
rs3025816	7747	GUGACGCAGCCCCUCGUGA	787	7747	GUGACGCAGCCCCUCGUGA	787	7765	UCACGAGGGGCUGCGUCAC	2539
rs3025816	7748	UGACGCAGCCCCUCGUGAU	788	7748	UGACGCAGCCCCUCGUGAU	788	7766	AUCACGAGGGGCUGCGUCA	2540
rs3025816	7749	GACGCAGCCCCUCGUGAUG	789	7749	GACGCAGCCCCUCGUGAUG	789	7767	CAUCACGAGGGGCUGCGUC	2541
rs3025816	7750	ACGCAGCCCCUCGUGAUGG	790	7750	ACGCAGCCCCUCGUGAUGG	790	7768	CCAUCACGAGGGGCUGCGU	2542
rs3025816	7751	CGCAGCCCCUCGUGAUGGA	791	7751	CGCAGCCCCUCGUGAUGGA	791	7769	UCCAUCACGAGGGGCUGCG	2543
rs3025816	7752	GCAGCCCCUCGUGAUGGAG	792	7752	GCAGCCCCUCGUGAUGGAG	792	7770	CUCCAUCACGAGGGGCUGC	2544
rs3025816	7753	CAGCCCCUCGUGAUGGAGC	793	7753	CAGCCCCUCGUGAUGGAGC	793	7771	GCUCCAUCACGAGGGGCUG	2545
rs3025816	7735	CUUGGUGUCCUGGUGACGU	794	7735	CUUGGUGUCCUGGUGACGU	794	7753	ACGUCACCAGGACACCAAG	2546
rs3025816	7736	UUGGUGUCCUGGUGACGUA	795	7736	UUGGUGUCCUGGUGACGUA	795	7754	UACGUCACCAGGACACCAA	2547
rs3025816	7737	UGGUGUCCUGGUGACGUAG	796	7737	UGGUGUCCUGGUGACGUAG	796	7755	CUACGUCACCAGGACACCA	2548
rs3025816	7738	GGUGUCCUGGUGACGUAGC	797	7738	GGUGUCCUGGUGACGUAGC	797	7756	GCUACGUCACCAGGACACC	2549
rs3025816	7739	GUGUCCUGGUGACGUAGCC	798	7739	GUGUCCUGGUGACGUAGCC	798	7757	GGCUACGUCACCAGGACAC	2550
rs3025816	7740	UGUCCUGGUGACGUAGCCC	799	7740	UGUCCUGGUGACGUAGCCC	799	7758	GGGCUACGUCACCAGGACA	2551
rs3025816	7741	GUCCUGGUGACGUAGCCCC	800	7741	GUCCUGGUGACGUAGCCCC	800	7759	GGGGCUACGUCACCAGGAC	2552
rs3025816	7742	UCCUGGUGACGUAGCCCCU	801	7742	UCCUGGUGACGUAGCCCCU	801	7760	AGGGGCUACGUCACCAGGA	2553
rs3025816	7743	CCUGGUGACGUAGCCCCUC	802	7743	CCUGGUGACGUAGCCCCUC	802	7761	GAGGGGCUACGUCACCAGG	2554
rs3025816	7744	CUGGUGACGUAGCCCCUCG	803	7744	CUGGUGACGUAGCCCCUCG	803	7762	CGAGGGGCUACGUCACCAG	2555
rs3025816	7745	UGGUGACGUAGCCCCUCGU	804	7745	UGGUGACGUAGCCCCUCGU	804	7763	ACGAGGGGCUACGUCACCA	2556
rs3025816	7746	GGUGACGUAGCCCCUCGUG	805	7746	GGUGACGUAGCCCCUCGUG	805	7764	CACGAGGGGCUACGUCACC	2557
rs3025816	7747	GUGACGUAGCCCCUCGUGA	806	7747	GUGACGUAGCCCCUCGUGA	806	7765	UCACGAGGGGCUACGUCAC	2558
rs3025816	7748	UGACGUAGCCCCUCGUGAU	807	7748	UGACGUAGCCCCUCGUGAU	807	7766	AUCACGAGGGGCUACGUCA	2559
rs3025816	7749	GACGUAGCCCCUCGUGAUG	808	7749	GACGUAGCCCCUCGUGAUG	808	7767	CAUCACGAGGGGCUACGUC	2560
rs3025816	7750	ACGUAGCCCCUCGUGAUGG	809	7750	ACGUAGCCCCUCGUGAUGG	809	7768	CCAUCACGAGGGGCUACGU	2561
rs3025816	7751	CGUAGCCCCUCGUGAUGGA	810	7751	CGUAGCCCCUCGUGAUGGA	810	7769	UCCAUCACGAGGGGCUACG	2562
rs3025816	7752	GUAGCCCCUCGUGAUGGAG	811	7752	GUAGCCCCUCGUGAUGGAG	811	7770	CUCCAUCACGAGGGGCUAC	2563
rs3025816	7753	UAGCCCCUCGUGAUGGAGC	812	7753	UAGCCCCUCGUGAUGGAGC	812	7771	GCUCCAUCACGAGGGGCUA	2564
rs3025814	7831	CAGGCCAUCACCUCACUGG	813	7831	CAGGCCAUCACCUCACUGG	813	7849	CCAGUGAGGUGAUGGCCUG	2565
rs3025814	7832	AGGCCAUCACCUCACUGGU	814	7832	AGGCCAUCACCUCACUGGU	814	7850	ACCAGUGAGGUGAUGGCCU	2566
rs3025814	7833	GGCCAUCACCUCACUGGUG	815	7833	GGCCAUCACCUCACUGGUG	815	7851	CACCAGUGAGGUGAUGGCC	2567

nucleotides are LNA nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA are alternatively 2'-methoxyethyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-methoxyethyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-methoxyethyl purine nucleotides). In another embodiment, any modified nucleotides present in the single stranded siNA molecules of the invention comprise modified nucleotides having properties or characteristics similar to naturally occurring ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the single stranded siNA molecules of the invention are preferably resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi.

In one embodiment, the invention features a method for modulating the expression of a RE gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the RE gene; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the RE gene in the cell.

In one embodiment, the invention features a method for modulating the expression of a RE gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the RE gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the RE gene in the cell.

In another embodiment, the invention features a method for modulating the expression of more than one RE gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the RE genes; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the RE genes in the cell.

In another embodiment, the invention features a method for modulating the expression of two or more RE genes within a cell comprising: (a) synthesizing one or more siNA molecules of the invention, which can be chemically-modified, wherein the siNA strands comprise sequences complementary to RNA of the RE genes and wherein the sense strand sequences of the siNAs comprise sequences identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the RE genes in the cell.

In another embodiment, the invention features a method for modulating the expression of more than one RE gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the RE gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the RE genes in the cell.

In one embodiment, siNA molecules of the invention are used as reagents in ex vivo applications. For example, siNA reagents are intoduced into tissue or cells that are transplanted into a subject for therapeutic effect. The cells and/or tissue can be derived from an organism or subject that later receives the explant, or can be derived from another organism or subject prior to transplantation. The siNA molecules can be used to modulate the expression of one or more genes in the cells or tissue, such that the cells or tissue obtain a desired phenotype or are able to perform a function when transplanted in vivo. In one embodiment, certain target cells from a patient are extracted. These extracted cells are contacted with siNAs targeteing a specific nucleotide sequence within the cells under conditions suitable for uptake of the siNAs by these cells (e.g. using delivery reagents such as cationic lipids, liposomes and the like or using techniques such as electroporation to facilitate the delivery of siNAs into cells). The cells are then reintroduced back into the same patient or other patients. In one embodiment, the invention features a method of modulating the expression of a RE gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the RE gene; and (b) introducing the siNA molecule into a

cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the RE gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the RE gene in that organism.

In one embodiment, the invention features a method of modulating the expression of a RE gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the RE gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the RE gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the RE gene in that organism.

In another embodiment, the invention features a method of modulating the expression of more than one RE gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the RE genes; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the RE genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the RE genes in that organism.

In one embodiment, the invention features a method of modulating the expression of a RE gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the RE gene; and (b) introducing the siNA molecule into the organism under conditions suitable to modulate the expression of

the RE gene in the organism. The level of RE protein or RNA can be determined as is known in the art.

In another embodiment, the invention features a method of modulating the expression of more than one RE gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the RE genes; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the RE genes in the organism. The level of RE protein or RNA can be determined as is known in the art.

In one embodiment, the invention features a method for modulating the expression of a RE gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the RE gene; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the RE gene in the cell.

In another embodiment, the invention features a method for modulating the expression of more than one RE gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the RE gene; and (b) contacting the cell in vitro or in vivo with the siNA molecule under conditions suitable to modulate the expression of the RE genes in the cell.

In one embodiment, the invention features a method of modulating the expression of a RE gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the RE gene; and (b) contacting the cell of the tissue explant derived from a particular organism with the siNA molecule under conditions suitable to modulate the expression of the RE gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the RE gene in that organism.

In another embodiment, the invention features a method of modulating the expression of more than one RE gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the RE gene; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the RE genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the RE genes in that organism.

In one embodiment, the invention features a method of modulating the expression of a RE gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the RE gene; and (b) introducing the siNA molecule into the organism under conditions suitable to modulate the expression of the RE gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one RE gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the RE gene; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the RE genes in the organism.

In one embodiment, the invention features a method of modulating the expression of a RE gene in an organism comprising contacting the organism with a siNA molecule of the invention under conditions suitable to modulate the expression of the RE gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one RE gene in an organism comprising contacting the organism with one or more siNA molecules of the invention under conditions suitable to modulate the expression of the RE genes in the organism.

The siNA molecules of the invention can be designed to down regulate or inhibit target (RE) gene expression through RNAi targeting of a variety of RNA molecules. In one embodiment, the siNA molecules of the invention are used to target various RNAs corresponding to a target gene. Non-limiting examples of such RNAs include messenger RNA (mRNA), alternate RNA splice variants of target gene(s), post-transcriptionally modified RNA of target gene(s), pre-mRNA of target gene(s), and/or RNA templates. If alternate splicing produces a family of transcripts that are distinguished by usage of appropriate exons, the instant invention can be used to inhibit gene expression through the appropriate exons to specifically inhibit or to distinguish among the functions of gene family members. For example, a protein that contains an alternatively spliced transmembrane domain can be expressed in both membrane bound and secreted forms. Use of the invention to target the exon containing the transmembrane domain can be used to determine the functional consequences of pharmaceutical targeting of membrane bound as opposed to the secreted form of the protein. Non-limiting examples of applications of the invention relating to targeting these RNA molecules include therapeutic pharmaceutical applications, pharmaceutical discovery applications, molecular diagnostic and gene function applications, and gene mapping, for example using single nucleotide polymorphism mapping with siNA molecules of the invention. Such applications can be implemented using known gene sequences or from partial sequences available from an expressed sequence tag (EST).

In another embodiment, the siNA molecules of the invention are used to target conserved sequences corresponding to a gene family or gene families such as RE family genes. As such, siNA molecules targeting multiple RE targets can provide increased therapeutic effect. In addition, siNA can be used to characterize pathways of gene function in a variety of applications. For example, the present invention can be used to inhibit the activity of target gene(s) in a pathway to determine the function of uncharacterized gene(s) in gene function analysis, mRNA function analysis, or translational analysis. The invention can be used to determine potential target gene pathways involved in various diseases and conditions toward pharmaceutical development. The invention can be used to understand pathways of gene expression involved in, for example, the progression and/or maintenance of cancer.

In one embodiment, siNA molecule(s) and/or methods of the invention are used to down regulate the expression of gene(s) that encode RNA referred to by Genbank Accession, for example RE genes encoding RNA sequence(s) referred to herein by Genbank Accession number, for example, Genbank Accession Nos. shown in **Table I**.

In one embodiment, the invention features a method comprising: (a) generating a library of siNA constructs having a predetermined complexity; and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target RNA sequence. In one embodiment, the siNA molecules of (a) have strands of a fixed length, for example, about 23 nucleotides in length. In another embodiment, the siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (*e.g.*, about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNAse protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

In one embodiment, the invention features a method comprising: (a) generating a randomized library of siNA constructs having a predetermined complexity, such as of 4^N, where N represents the number of base paired nucleotides in each of the siNA construct strands (*eg.* for a siNA construct having 21 nucleotide sense and antisense strands with 19 base pairs, the complexity would be 4^{19}); and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target RE RNA sequence. In another embodiment, the siNA molecules of (a) have strands of a fixed length, for example about 23 nucleotides in length. In yet another embodiment, the siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (*e.g.*, about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described in Example 7 herein. In another embodiment, the assay can comprise a cell culture system

in which target RNA is expressed. In another embodiment, fragments of RE RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNAse protection assays, to determine the most suitable target site(s) within the target RE RNA sequence. The target RE RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

In another embodiment, the invention features a method comprising: (a) analyzing the sequence of a RNA target encoded by a target gene; (b) synthesizing one or more sets of siNA molecules having sequence complementary to one or more regions of the RNA of (a); and (c) assaying the siNA molecules of (b) under conditions suitable to determine RNAi targets within the target RNA sequence. In one embodiment, the siNA molecules of (b) have strands of a fixed length, for example about 23 nucleotides in length. In another embodiment, the siNA molecules of (b) are of differing length, for example having strands of about 19 to about 25 (*e.g.*, about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. Fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNAse protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by expression in *in vivo* systems.

By "target site" is meant a sequence within a target RNA that is "targeted" for cleavage mediated by a siNA construct which contains sequences within its antisense region that are complementary to the target sequence.

By "detectable level of cleavage" is meant cleavage of target RNA (and formation of cleaved product RNAs) to an extent sufficient to discern cleavage products above the background of RNAs produced by random degradation of the target RNA. Production of cleavage products from 1-5% of the target RNA is sufficient to detect above the background for most methods of detection.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention, which can be chemically-modified, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising siNA molecules of the invention, which can be chemically-modified, targeting one or more genes in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a method for diagnosing a disease or condition in a subject comprising administering to the subject a composition of the invention under conditions suitable for the diagnosis of the disease or condition in the subject. In another embodiment, the invention features a method for treating or preventing a disease or condition in a subject, comprising administering to the subject a composition of the invention under conditions suitable for the treatment or prevention of the disease or condition in the subject, alone or in conjunction with one or more other therapeutic compounds. In yet another embodiment, the invention features a method for reducing or preventing tissue rejection in a subject comprising administering to the subject a composition of the invention under conditions suitable for the reduction or prevention of tissue rejection in the subject.

In another embodiment, the invention features a method for validating a RE gene target, comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a RE target gene; (b) introducing the siNA molecule into a cell, tissue, or organism under conditions suitable for modulating expression of the RE target gene in the cell, tissue, or organism; and (c) determining the function of the gene by assaying for any phenotypic change in the cell, tissue, or organism.

In another embodiment, the invention features a method for validating a RE target comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a RE target gene; (b) introducing the siNA molecule into a biological system under conditions suitable for modulating expression of the RE target gene in the biological system; and (c) determining the function of the gene by assaying for any phenotypic change in the biological system.

By "biological system" is meant, material, in a purified or unpurified form, from biological sources, including but not limited to human or animal, wherein the system comprises the components required for RNAi acitivity. The term "biological system" includes, for example, a cell, tissue, or organism, or extract thereof. The term biological system also includes reconstituted RNAi systems that can be used in an *in vitro* setting.

By "phenotypic change" is meant any detectable change to a cell that occurs in response to contact or treatment with a nucleic acid molecule of the invention (e.g., siNA). Such detectable changes include, but are not limited to, changes in shape, size, proliferation, motility, protein expression or RNA expression or other physical or chemical changes as can be assayed by methods known in the art. The detectable change can also include expression of reporter genes/molecules such as Green Florescent Protein (GFP) or various tags that are used to identify an expressed protein or any other cellular component that can be assayed.

In one embodiment, the invention features a kit containing a siNA molecule of the invention, which can be chemically-modified, that can be used to modulate the expression of a RE target gene in a biological system, including, for example, in a cell, tissue, or organism. In another embodiment, the invention features a kit containing more than one siNA molecule of the invention, which can be chemically-modified, that can be used to modulate the expression of more than one RE target gene in a biological system, including, for example, in a cell, tissue, or organism.

In one embodiment, the invention features a cell containing one or more siNA molecules of the invention, which can be chemically-modified. In another embodiment, the cell containing a siNA molecule of the invention is a mammalian cell. In yet another embodiment, the cell containing a siNA molecule of the invention is a human cell.

In one embodiment, the synthesis of a siNA molecule of the invention, which can be chemically-modified, comprises: (a) synthesis of two complementary strands of the siNA molecule; (b) annealing the two complementary strands together under conditions suitable to obtain a double-stranded siNA molecule. In another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase oligonucleotide

synthesis. In yet another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase tandem oligonucleotide synthesis.

In one embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing a first oligonucleotide sequence strand of the siNA molecule, wherein the first oligonucleotide sequence strand comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of the second oligonucleotide sequence strand of the siNA; (b) synthesizing the second oligonucleotide sequence strand of siNA on the scaffold of the first oligonucleotide sequence strand, wherein the second oligonucleotide sequence strand further comprises a chemical moiety than can be used to purify the siNA duplex; (c) cleaving the linker molecule of (a) under conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex; and (d) purifying the siNA duplex utilizing the chemical moiety of the second oligonucleotide sequence strand. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions using an alkylamine base such as methylamine. In one embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place concomitantly. In another embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group, which can be employed in a trityl-on synthesis strategy as described herein. In yet another embodiment, the chemical moiety, such as a dimethoxytrityl group, is removed during purification, for example, using acidic conditions.

In a further embodiment, the method for siNA synthesis is a solution phase synthesis or hybrid phase synthesis wherein both strands of the siNA duplex are synthesized in tandem using a cleavable linker attached to the first sequence which acts a scaffold for synthesis of the second sequence. Cleavage of the linker under conditions

suitable for hybridization of the separate siNA sequence strands results in formation of the double-stranded siNA molecule.

In another embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing one oligonucleotide sequence strand of the siNA molecule, wherein the sequence comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of another oligonucleotide sequence; (b) synthesizing a second oligonucleotide sequence having complementarity to the first sequence strand on the scaffold of (a), wherein the second sequence comprises the other strand of the double-stranded siNA molecule and wherein the second sequence further comprises a chemical moiety than can be used to isolate the attached oligonucleotide sequence; (c) purifying the product of (b) utilizing the chemical moiety of the second oligonucleotide sequence strand under conditions suitable for isolating the full-length sequence comprising both siNA oligonucleotide strands connected by the cleavable linker and under conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions. In another embodiment, cleavage of the linker molecule in (c) above takes place after deprotection of the oligonucleotide. In another embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity or differing reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place either concomitantly or sequentially. In one embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group.

In another embodiment, the invention features a method for making a double-stranded siNA molecule in a single synthetic process comprising: (a) synthesizing an oligonucleotide having a first and a second sequence, wherein the first sequence is complementary to the second sequence, and the first oligonucleotide sequence is linked

to the second sequence via a cleavable linker, and wherein a terminal 5'-protecting group, for example, a 5'-O-dimethoxytrityl group (5'-O-DMT) remains on the oligonucleotide having the second sequence; (b) deprotecting the oligonucleotide whereby the deprotection results in the cleavage of the linker joining the two oligonucleotide sequences; and (c) purifying the product of (b) under conditions suitable for isolating the double-stranded siNA molecule, for example using a trityl-on synthesis strategy as described herein.

In another embodiment, the method of synthesis of siNA molecules of the invention comprises the teachings of Scaringe *et al.*, US Patent Nos. 5,889,136; 6,008,400; and 6,111,086, incorporated by reference herein in their entirety.

In one embodiment, the invention features siNA constructs that mediate RNAi against a RE, wherein the siNA construct comprises one or more chemical modifications, for example, one or more chemical modifications having any of Formulae I-VII or any combination thereof that increases the nuclease resistance of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased nuclease resistance comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased nuclease resistance.

In one embodiment, the invention features siNA constructs that mediate RNAi against a RE, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the sense and antisense strands of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the sense and antisense strands of the siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the sense and antisense strands of the siNA molecule.

In one embodiment, the invention features siNA constructs that mediate RNAi against a RE, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target RNA sequence within a cell.

In one embodiment, the invention features siNA constructs that mediate RNAi against a RE, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target DNA sequence within a cell.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence.

In one embodiment, the invention features siNA constructs that mediate RNAi against a RE, wherein the siNA construct comprises one or more chemical modifications described herein that modulate the polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA construct.

In another embodiment, the invention features a method for generating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase

capable of generating additional endogenous siNA molecules having sequence homology to a chemically-modified siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA molecule.

In one embodiment, the invention features chemically-modified siNA constructs that mediate RNAi against a RE in a cell, wherein the chemical modifications do not significantly effect the interaction of siNA with a target RNA molecule, DNA molecule and/or proteins or other factors that are essential for RNAi in a manner that would decrease the efficacy of RNAi mediated by such siNA constructs.

In another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against RE comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity.

In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against a RE target RNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target RNA.

In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against a RE target DNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target DNA.

In one embodiment, the invention features siNA constructs that mediate RNAi against a RE, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the cellular uptake of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules against RE with improved cellular uptake comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved cellular uptake.

In one embodiment, the invention features siNA constructs that mediate RNAi against a RE, wherein the siNA construct comprises one or more chemical modifications described herein that increases the bioavailability of the siNA construct, for example, by attaching polymeric conjugates such as polyethyleneglycol or equivalent conjugates that improve the pharmacokinetics of the siNA construct, or by attaching conjugates that target specific tissue types or cell types *in vivo*. Non-limiting examples of such conjugates are described in Vargeese *et al.*, U.S. Serial No. 10/201,394 incorporated by reference herein.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability, comprising (a) introducing a conjugate into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability. Such conjugates can include ligands for cellular receptors, such as peptides derived from naturally occurring protein ligands; protein localization sequences, including cellular ZIP code sequences; antibodies; nucleic acid aptamers; vitamins and other co-factors, such as folate and N-acetylgalactosamine; polymers, such as polyethyleneglycol (PEG); phospholipids; cholesterol; polyamines, such as spermine or spermidine; and others.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically

modified in a manner that it can no longer act as a guide sequence for efficiently mediating RNA interference and/or be recognized by cellular proteins that facilitate RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein the second sequence is designed or modified in a manner that prevents its entry into the RNAi pathway as a guide sequence or as a sequence that is complementary to a target nucleic acid (e.g., RNA) sequence. Such design or modifications are expected to enhance the activity of siNA and/or improve the specificity of siNA molecules of the invention. These modifications are also expected to minimize any off-target effects and/or associated toxicity.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is incapable of acting as a guide sequence for mediating RNA interference.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence does not have a terminal 5'-hydroxyl (5'-OH) or 5'-phosphate group.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a terminal cap moiety at the 5'-end of said second sequence. In one embodiment, the terminal cap moiety comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in **Figure 10**, an alkyl or cycloalkyl group, a

heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a terminal cap moiety at the 5'-end and 3'-end of said second sequence. In one embodiment, each terminal cap moiety individually comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in **Figure 10**, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising (a) introducing one or more chemical modifications into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved specificity. In another embodiment, the chemical modification used to improve specificity comprises terminal cap modifications at the 5'-end, 3'-end, or both 5' and 3'-ends of the siNA molecule. The terminal cap modifications can comprise, for example, structures shown in **Figure 10** (e.g. inverted deoxyabasic moieties) or any other chemical modification that renders a portion of the siNA molecule (e.g. the sense strand) incapable of mediating RNA interference against an off target nucleic acid sequence. In a non-limiting example, a siNA molecule is designed such that only the antisense sequence of the siNA molecule can serve as a guide sequence for RISC mediated degradation of a corresponding target RNA sequence. This can be accomplished by rendering the sense sequence of the siNA inactive by introducing chemical modifications to the sense strand that preclude recognition of the sense strand as a guide sequence by RNAi machinery. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand of the siNA, or any other group that serves to render the sense strand inactive as a guide sequence for mediating RNA interference. These modifications, for

example, can result in a molecule where the 5'-end of the sense strand no longer has a free 5'-hydroxyl (5'-OH) or a free 5'-phosphate group (e.g., phosphate, diphosphate, triphosphate, cyclic phosphate etc.). Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22" chemistries and variants thereof wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising introducing one or more chemical modifications into the structure of a siNA molecule that prevent a strand or portion of the siNA molecule from acting as a template or guide sequence for RNAi acitivity. In one embodiment, the inactive strand or sense region of the siNA molecule is the sense strand or sense region of the siNA molecule, i.e. the strand or region of the siNA that does not have complementarity to the target nucleic acid sequence. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand or region of the siNA that does not comprise a 5'-hydroxyl (5'-OH) or 5'-phosphate group, or any other group that serves to render the sense strand or sense region inactive as a guide sequence for mediating RNA interference. Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22"chemistries and variants thereof wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

In one embodiment, the invention features a method for screening siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of unmodified siNA molecules, (b) screening the siNA molecules of step (a) under conditions suitable for isolating siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence, and (c) introducing chemical modifications (e.g. chemical modifications as described herein or as otherwise known in the art) into the active siNA molecules of (b). In one embodiment, the method further comprises re-screening the chemically modified siNA molecules of step (c) under conditions suitable for isolating chemically modified siNA

molecules that are active in mediating RNA interference against the target nucleic acid sequence.

In one embodiment, the invention features a method for screening chemically modified siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of chemically modified siNA molecules (e.g. siNA molecules as described herein or as otherwise known in the art), and (b) screening the siNA molecules of step (a) under conditions suitable for isolating chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

The term "ligand" refers to any compound or molecule, such as a drug, peptide, hormone, or neurotransmitter, that is capable of interacting with another compound, such as a receptor, either directly or indirectly. The receptor that interacts with a ligand can be present on the surface of a cell or can alternately be an intercullular receptor. Interaction of the ligand with the receptor can result in a biochemical reaction, or can simply be a physical interaction or association.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing an excipient formulation to a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability. Such excipients include polymers such as cyclodextrins, lipids, cationic lipids, polyamines, phospholipids, nanoparticles, receptors, ligands, and others.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing nucleotides having any of Formulae I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability.

In another embodiment, polyethylene glycol (PEG) can be covalently attached to siNA compounds of the present invention. The attached PEG can be any molecular weight, preferably from about 2,000 to about 50,000 daltons (Da).

The present invention can be used alone or as a component of a kit having at least one of the reagents necessary to carry out the *in vitro* or *in vivo* introduction of RNA to test samples and/or subjects. For example, preferred components of the kit include a siNA molecule of the invention and a vehicle that promotes introduction of the siNA into cells of interest as described herein (e.g., using lipids and other methods of transfection known in the art, see for example Beigelman *et al,* US 6,395,713). The kit can be used for target validation, such as in determining gene function and/or activity, or in drug optimization, and in drug discovery (see for example Usman et al., USSN 60/402,996). Such a kit can also include instructions to allow a user of the kit to practice the invention.

The term "short interfering nucleic acid", "siNA", "short interfering RNA", "siRNA", "short interfering nucleic acid molecule", "short interfering oligonucleotide molecule", or "chemically-modified short interfering nucleic acid molecule" as used herein refers to any nucleic acid molecule capable of inhibiting or down regulating gene expression or viral replication, for example by mediating RNA interference "RNAi" or gene silencing in a sequence-specific manner; see for example Zamore *et al.,* 2000, Cell, 101, 25-33; Bass, 2001, *Nature*, 411, 428-429; Elbashir *et al.,* 2001, *Nature*, 411, 494-498; and Kreutzer *et al.,* International PCT Publication No. WO 00/44895; Zernicka-Goetz *et al.,* International PCT Publication No. WO 01/36646; Fire, International PCT Publication No. WO 99/32619; Plaetinck *et al.,* International PCT Publication No. WO 00/01846; Mello and Fire, International PCT Publication No. WO 01/29058; Deschamps-Depaillette, International PCT Publication No. WO 99/07409; and Li *et al.,* International PCT Publication No. WO 00/44914; Allshire, 2002, *Science,* 297, 1818-1819; Volpe *et al.,* 2002, *Science,* 297, 1833-1837; Jenuwein, 2002, *Science,* 297, 2215-2218; and Hall *et al.,* 2002, *Science,* 297, 2232-2237; Hutvagner and Zamore, 2002, *Science*, 297, 2056-60; McManus *et al.,* 2002, *RNA*, 8, 842-850; Reinhart *et al.,* 2002, *Gene & Dev.,* 16, 1616-1626; and Reinhart & Bartel, 2002, *Science*, 297, 1831). Non limiting examples of siNA molecules of the invention are shown in **Figures 4-6,** and **Tables II and III** herein. For example the siNA can be a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a

rs3025814	7834	GCCAUCACCUCACUGGUGC	816	7834	GCCAUCACCUCACUGGUGC	816	7852	GCACCAGUGAGGUGAUGGC	2568
rs3025814	7835	CCAUCACCUCACUGGUGCU	817	7835	CCAUCACCUCACUGGUGCU	817	7853	AGCACCAGUGAGGUGAUGG	2569
rs3025814	7836	CAUCACCUCACUGGUGCUC	818	7836	CAUCACCUCACUGGUGCUC	818	7854	GAGCACCAGUGAGGUGAUG	2570
rs3025814	7837	AUCACCUCACUGGUGCUCA	819	7837	AUCACCUCACUGGUGCUCA	819	7855	UGAGCACCAGUGAGGUGAU	2571
rs3025814	7838	UCACCUCACUGGUGCUCAG	820	7838	UCACCUCACUGGUGCUCAG	820	7856	CUGAGCACCAGUGAGGUGA	2572
rs3025814	7839	CACCUCACUGGUGCUCAGU	821	7839	CACCUCACUGGUGCUCAGU	821	7857	ACUGAGCACCAGUGAGGUG	2573
rs3025814	7840	ACCUCACUGGUGCUCAGUG	822	7840	ACCUCACUGGUGCUCAGUG	822	7858	CACUGAGCACCAGUGAGGU	2574
rs3025814	7841	CCUCACUGGUGCUCAGUGC	823	7841	CCUCACUGGUGCUCAGUGC	823	7859	GCACUGAGCACCAGUGAGG	2575
rs3025814	7842	CUCACUGGUGCUCAGUGCA	824	7842	CUCACUGGUGCUCAGUGCA	824	7860	UGCACUGAGCACCAGUGAG	2576
rs3025814	7843	UCACUGGUGCUCAGUGCAA	825	7843	UCACUGGUGCUCAGUGCAA	825	7861	UUGCACUGAGCACCAGUGA	2577
rs3025814	7844	CACUGGUGCUCAGUGCAAU	826	7844	CACUGGUGCUCAGUGCAAU	826	7862	AUUGCACUGAGCACCAGUG	2578
rs3025814	7845	ACUGGUGCUCAGUGCAAUG	827	7845	ACUGGUGCUCAGUGCAAUG	827	7863	CAUUGCACUGAGCACCAGU	2579
rs3025814	7846	CUGGUGCUCAGUGCAAUGA	828	7846	CUGGUGCUCAGUGCAAUGA	828	7864	UCAUUGCACUGAGCACCAG	2580
rs3025814	7847	UGGUGCUCAGUGCAAUGAC	829	7847	UGGUGCUCAGUGCAAUGAC	829	7865	GUCAUUGCACUGAGCACCA	2581
rs3025814	7848	GGUGCUCAGUGCAAUGACU	830	7848	GGUGCUCAGUGCAAUGACU	830	7866	AGUCAUUGCACUGAGCACC	2582
rs3025814	7849	GUGCUCAGUGCAAUGACUG	831	7849	GUGCUCAGUGCAAUGACUG	831	7867	CAGUCAUUGCACUGAGCAC	2583
rs3025814	7831	CAGGCCAUCACCUCACUGC	832	7831	CAGGCCAUCACCUCACUGC	832	7849	GCAGUGAGGUGAUGGCCUG	2584
rs3025814	7832	AGGCCAUCACCUCACUGCU	833	7832	AGGCCAUCACCUCACUGCU	833	7850	AGCAGUGAGGUGAUGGCCU	2585
rs3025814	7833	GGCCAUCACCUCACUGCUG	834	7833	GGCCAUCACCUCACUGCUG	834	7851	CAGCAGUGAGGUGAUGGCC	2586
rs3025814	7834	GCCAUCACCUCACUGCUGC	835	7834	GCCAUCACCUCACUGCUGC	835	7852	GCAGCAGUGAGGUGAUGGC	2587
rs3025814	7835	CCAUCACCUCACUGCUGCU	836	7835	CCAUCACCUCACUGCUGCU	836	7853	AGCAGCAGUGAGGUGAUGG	2588
rs3025814	7836	CAUCACCUCACUGCUGCUC	837	7836	CAUCACCUCACUGCUGCUC	837	7854	GAGCAGCAGUGAGGUGAUG	2589
rs3025814	7837	AUCACCUCACUGCUGCUCA	838	7837	AUCACCUCACUGCUGCUCA	838	7855	UGAGCAGCAGUGAGGUGAU	2590
rs3025814	7838	UCACCUCACUGCUGCUCAG	839	7838	UCACCUCACUGCUGCUCAG	839	7856	CUGAGCAGCAGUGAGGUGA	2591
rs3025814	7839	CACCUCACUGCUGCUCAGU	840	7839	CACCUCACUGCUGCUCAGU	840	7857	ACUGAGCAGCAGUGAGGUG	2592
rs3025814	7840	ACCUCACUGCUGCUCAGUG	841	7840	ACCUCACUGCUGCUCAGUG	841	7858	CACUGAGCAGCAGUGAGGU	2593
rs3025814	7841	CCUCACUGCUGCUCAGUGC	842	7841	CCUCACUGCUGCUCAGUGC	842	7859	GCACUGAGCAGCAGUGAGG	2594
rs3025814	7842	CUCACUGCUGCUCAGUGCA	843	7842	CUCACUGCUGCUCAGUGCA	843	7860	UGCACUGAGCAGCAGUGAG	2595
rs3025814	7843	UCACUGCUGCUCAGUGCAA	844	7843	UCACUGCUGCUCAGUGCAA	844	7861	UUGCACUGAGCAGCAGUGA	2596
rs3025814	7844	CACUGCUGCUCAGUGCAAU	845	7844	CACUGCUGCUCAGUGCAAU	845	7862	AUUGCACUGAGCAGCAGUG	2597
rs3025814	7845	ACUGCUGCUCAGUGCAAUG	846	7845	ACUGCUGCUCAGUGCAAUG	846	7863	CAUUGCACUGAGCAGCAGU	2598
rs3025814	7846	CUGCUGCUCAGUGCAAUGA	847	7846	CUGCUGCUCAGUGCAAUGA	847	7864	UCAUUGCACUGAGCAGCAG	2599
rs3025814	7847	UGCUGCUCAGUGCAAUGAC	848	7847	UGCUGCUCAGUGCAAUGAC	848	7865	GUCAUUGCACUGAGCAGCA	2600
rs3025814	7848	GCUGCUCAGUGCAAUGACU	849	7848	GCUGCUCAGUGCAAUGACU	849	7866	AGUCAUUGCACUGAGCAGC	2601
rs3025814	7849	CUGCUCAGUGCAAUGACUG	850	7849	CUGCUCAGUGCAAUGACUG	850	7867	CAGUCAUUGCACUGAGCAG	2602
rs362273	8100	CCACGAGAAGCUGCUGCUA	851	8100	CCACGAGAAGCUGCUGCUA	851	8118	UAGCAGCAGCUUCUCGUGG	2603
rs362273	8101	CACGAGAAGCUGCUGCUAC	852	8101	CACGAGAAGCUGCUGCUAC	852	8119	GUAGCAGCAGCUUCUCGUG	2604
rs362273	8102	ACGAGAAGCUGCUGCUACA	853	8102	ACGAGAAGCUGCUGCUACA	853	8120	UGUAGCAGCAGCUUCUCGU	2605
rs362273	8103	CGAGAAGCUGCUGCUACAG	854	8103	CGAGAAGCUGCUGCUACAG	854	8121	CUGUAGCAGCAGCUUCUCG	2606

rs362273	8104	GAGAAGCUGCUGCUACAGA	855	8104	GAGAAGCUGCUGCUACAGA	855	8122	UCUGUAGCAGCAGCUUCUC	2607
rs362273	8105	AGAAGCUGCUGCUACAGAU	856	8105	AGAAGCUGCUGCUACAGAU	856	8123	AUCUGUAGCAGCAGCUUCU	2608
rs362273	8106	GAAGCUGCUGCUACAGAUC	857	8106	GAAGCUGCUGCUACAGAUC	857	8124	GAUCUGUAGCAGCAGCUUC	2609
rs362273	8107	AAGCUGCUGCUACAGAUCA	858	8107	AAGCUGCUGCUACAGAUCA	858	8125	UGAUCUGUAGCAGCAGCUU	2610
rs362273	8108	AGCUGCUGCUACAGAUCAA	859	8108	AGCUGCUGCUACAGAUCAA	859	8126	UUGAUCUGUAGCAGCAGCU	2611
rs362273	8109	GCUGCUGCUACAGAUCAAC	860	8109	GCUGCUGCUACAGAUCAAC	860	8127	GUUGAUCUGUAGCAGCAGC	2612
rs362273	8110	CUGCUGCUACAGAUCAACC	861	8110	CUGCUGCUACAGAUCAACC	861	8128	GGUUGAUCUGUAGCAGCAG	2613
rs362273	8111	UGCUGCUACAGAUCAACCC	862	8111	UGCUGCUACAGAUCAACCC	862	8129	GGGUUGAUCUGUAGCAGCA	2614
rs362273	8112	GCUGCUACAGAUCAACCCC	863	8112	GCUGCUACAGAUCAACCCC	863	8130	GGGGUUGAUCUGUAGCAGC	2615
rs362273	8113	CUGCUACAGAUCAACCCCG	864	8113	CUGCUACAGAUCAACCCCG	864	8131	CGGGGUUGAUCUGUAGCAG	2616
rs362273	8114	UGCUACAGAUCAACCCCGA	865	8114	UGCUACAGAUCAACCCCGA	865	8132	UCGGGGUUGAUCUGUAGCA	2617
rs362273	8115	GCUACAGAUCAACCCCGAG	866	8115	GCUACAGAUCAACCCCGAG	866	8133	CUCGGGGUUGAUCUGUAGC	2618
rs362273	8116	CUACAGAUCAACCCCGAGC	867	8116	CUACAGAUCAACCCCGAGC	867	8134	GCUCGGGGUUGAUCUGUAG	2619
rs362273	8117	UACAGAUCAACCCCGAGCG	868	8117	UACAGAUCAACCCCGAGCG	868	8135	CGCUCGGGGUUGAUCUGUA	2620
rs362273	8118	ACAGAUCAACCCCGAGCGG	869	8118	ACAGAUCAACCCCGAGCGG	869	8136	CCGCUCGGGGUUGAUCUGU	2621
rs362273	8100	CCACGAGAAGCUGCUGCUG	870	8100	CCACGAGAAGCUGCUGCUG	870	8118	CAGCAGCAGCUUCUCGUGG	2622
rs362273	8101	CACGAGAAGCUGCUGCUGC	871	8101	CACGAGAAGCUGCUGCUGC	871	8119	GCAGCAGCAGCUUCUCGUG	2623
rs362273	8102	ACGAGAAGCUGCUGCUGCA	872	8102	ACGAGAAGCUGCUGCUGCA	872	8120	UGCAGCAGCAGCUUCUCGU	2624
rs362273	8103	CGAGAAGCUGCUGCUGCAG	873	8103	CGAGAAGCUGCUGCUGCAG	873	8121	CUGCAGCAGCAGCUUCUCG	2625
rs362273	8104	GAGAAGCUGCUGCUGCAGA	874	8104	GAGAAGCUGCUGCUGCAGA	874	8122	UCUGCAGCAGCAGCUUCUC	2626
rs362273	8105	AGAAGCUGCUGCUGCAGAU	875	8105	AGAAGCUGCUGCUGCAGAU	875	8123	AUCUGCAGCAGCAGCUUCU	2627
rs362273	8106	GAAGCUGCUGCUGCAGAUC	876	8106	GAAGCUGCUGCUGCAGAUC	876	8124	GAUCUGCAGCAGCAGCUUC	2628
rs362273	8107	AAGCUGCUGCUGCAGAUCA	877	8107	AAGCUGCUGCUGCAGAUCA	877	8125	UGAUCUGCAGCAGCAGCUU	2629
rs362273	8108	AGCUGCUGCUGCAGAUCAA	878	8108	AGCUGCUGCUGCAGAUCAA	878	8126	UUGAUCUGCAGCAGCAGCU	2630
rs362273	8109	GCUGCUGCUGCAGAUCAAC	879	8109	GCUGCUGCUGCAGAUCAAC	879	8127	GUUGAUCUGCAGCAGCAGC	2631
rs362273	8110	CUGCUGCUGCAGAUCAACC	880	8110	CUGCUGCUGCAGAUCAACC	880	8128	GGUUGAUCUGCAGCAGCAG	2632
rs362273	8111	UGCUGCUGCAGAUCAACCC	881	8111	UGCUGCUGCAGAUCAACCC	881	8129	GGGUUGAUCUGCAGCAGCA	2633
rs362273	8112	GCUGCUGCAGAUCAACCCC	882	8112	GCUGCUGCAGAUCAACCCC	882	8130	GGGGUUGAUCUGCAGCAGC	2634
rs362273	8113	CUGCUGCAGAUCAACCCCG	883	8113	CUGCUGCAGAUCAACCCCG	883	8131	CGGGGUUGAUCUGCAGCAG	2635
rs362273	8114	UGCUGCAGAUCAACCCCGA	884	8114	UGCUGCAGAUCAACCCCGA	884	8132	UCGGGGUUGAUCUGCAGCA	2636
rs362273	8115	GCUGCAGAUCAACCCCGAG	885	8115	GCUGCAGAUCAACCCCGAG	885	8133	CUCGGGGUUGAUCUGCAGC	2637
rs362273	8116	CUGCAGAUCAACCCCGAGC	886	8116	CUGCAGAUCAACCCCGAGC	886	8134	GCUCGGGGUUGAUCUGCAG	2638
rs362273	8117	UGCAGAUCAACCCCGAGCG	887	8117	UGCAGAUCAACCCCGAGCG	887	8135	CGCUCGGGGUUGAUCUGCA	2639
rs362273	8118	GCAGAUCAACCCCGAGCGG	888	8118	GCAGAUCAACCCCGAGCGG	888	8136	CCGCUCGGGGUUGAUCUGC	2640
HD-Ex58	8231	ACGAGGAAGAGGAGGAGGA	889	8231	ACGAGGAAGAGGAGGAGGA	889	8249	UCCUCCUCCUCUUCCUCGU	2641
HD-Ex58	8232	CGAGGAAGAGGAGGAGGAG	890	8232	CGAGGAAGAGGAGGAGGAG	890	8250	CUCCUCCUCCUCUUCCUCG	2642
HD-Ex58	8233	GAGGAAGAGGAGGAGGAGG	891	8233	GAGGAAGAGGAGGAGGAGG	891	8251	CCUCCUCCUCCUCUUCCUC	2643
HD-Ex58	8234	AGGAAGAGGAGGAGGAGGC	892	8234	AGGAAGAGGAGGAGGAGGC	892	8252	GCCUCCUCCUCCUCUUCCU	2644
HD-Ex58	8235	GGAAGAGGAGGAGGAGGCC	893	8235	GGAAGAGGAGGAGGAGGCC	893	8253	GGCCUCCUCCUCCUCUUCC	2645

HD-Ex58	8236	GAAGAGGAGGAGGAGGCCG	894	8236	GAAGAGGAGGAGGAGGCCG	894	8254	CGGCCUCCUCCUCCUCUUC	2646
HD-Ex58	8237	AAGAGGAGGAGGAGGCCGA	895	8237	AAGAGGAGGAGGAGGCCGA	895	8255	UCGGCCUCCUCCUCCUCUU	2647
HD-Ex58	8238	AGAGGAGGAGGAGGCCGAC	896	8238	AGAGGAGGAGGAGGCCGAC	896	8256	GUCGGCCUCCUCCUCCUCU	2648
HD-Ex58	8239	GAGGAGGAGGAGGCCGACG	897	8239	GAGGAGGAGGAGGCCGACG	897	8257	CGUCGGCCUCCUCCUCCUC	2649
HD-Ex58	8240	AGGAGGAGGAGGCCGACGC	898	8240	AGGAGGAGGAGGCCGACGC	898	8258	GCGUCGGCCUCCUCCUCCU	2650
HD-Ex58	8241	GGAGGAGGAGGCCGACGCC	899	8241	GGAGGAGGAGGCCGACGCC	899	8259	GGCGUCGGCCUCCUCCUCC	2651
HD-Ex58	8231	ACGAGGAAGAGGAGGAGGC	900	8231	ACGAGGAAGAGGAGGAGGC	900	8249	GCCUCCUCCUCUUCCUCGU	2652
HD-Ex58	8232	CGAGGAAGAGGAGGAGGCC	901	8232	CGAGGAAGAGGAGGAGGCC	901	8250	GGCCUCCUCCUCUUCCUCG	2653
HD-Ex58	8233	GAGGAAGAGGAGGAGGCCG	902	8233	GAGGAAGAGGAGGAGGCCG	902	8251	CGGCCUCCUCCUCUUCCUC	2654
HD-Ex58	8234	AGGAAGAGGAGGAGGCCGA	903	8234	AGGAAGAGGAGGAGGCCGA	903	8252	UCGGCCUCCUCCUCUUCCU	2655
HD-Ex58	8235	GGAAGAGGAGGAGGCCGAC	904	8235	GGAAGAGGAGGAGGCCGAC	904	8253	GUCGGCCUCCUCCUCUUCC	2656
HD-Ex58	8236	GAAGAGGAGGAGGCCGACG	905	8236	GAAGAGGAGGAGGCCGACG	905	8254	CGUCGGCCUCCUCCUCUUC	2657
HD-Ex58	8237	AAGAGGAGGAGGCCGACGC	906	8237	AAGAGGAGGAGGCCGACGC	906	8255	GCGUCGGCCUCCUCCUCUU	2658
HD-Ex58	8238	AGAGGAGGAGGCCGACGCC	907	8238	AGAGGAGGAGGCCGACGCC	907	8256	GGCGUCGGCCUCCUCCUCU	2659
rs2276881	8460	GCGCAACCAGUUUGAGCUG	908	8460	GCGCAACCAGUUUGAGCUG	908	8478	CAGCUCAAACUGGUUGCGC	2660
rs2276881	8461	CGCAACCAGUUUGAGCUGA	909	8461	CGCAACCAGUUUGAGCUGA	909	8479	UCAGCUCAAACUGGUUGCG	2661
rs2276881	8462	GCAACCAGUUUGAGCUGAU	910	8462	GCAACCAGUUUGAGCUGAU	910	8480	AUCAGCUCAAACUGGUUGC	2662
rs2276881	8463	CAACCAGUUUGAGCUGAUG	911	8463	CAACCAGUUUGAGCUGAUG	911	8481	CAUCAGCUCAAACUGGUUG	2663
rs2276881	8464	AACCAGUUUGAGCUGAUGU	912	8464	AACCAGUUUGAGCUGAUGU	912	8482	ACAUCAGCUCAAACUGGUU	2664
rs2276881	8465	ACCAGUUUGAGCUGAUGUA	913	8465	ACCAGUUUGAGCUGAUGUA	913	8483	UACAUCAGCUCAAACUGGU	2665
rs2276881	8466	CCAGUUUGAGCUGAUGUAU	914	8466	CCAGUUUGAGCUGAUGUAU	914	8484	AUACAUCAGCUCAAACUGG	2666
rs2276881	8467	CAGUUUGAGCUGAUGUAUG	915	8467	CAGUUUGAGCUGAUGUAUG	915	8485	CAUACAUCAGCUCAAACUG	2667
rs2276881	8468	AGUUUGAGCUGAUGUAUGU	916	8468	AGUUUGAGCUGAUGUAUGU	916	8486	ACAUACAUCAGCUCAAACU	2668
rs2276881	8469	GUUUGAGCUGAUGUAUGUG	917	8469	GUUUGAGCUGAUGUAUGUG	917	8487	CACAUACAUCAGCUCAAAC	2669
rs2276881	8470	UUUGAGCUGAUGUAUGUGA	918	8470	UUUGAGCUGAUGUAUGUGA	918	8488	UCACAUACAUCAGCUCAAA	2670
rs2276881	8471	UUGAGCUGAUGUAUGUGAC	919	8471	UUGAGCUGAUGUAUGUGAC	919	8489	GUCACAUACAUCAGCUCAA	2671
rs2276881	8472	UGAGCUGAUGUAUGUGACG	920	8472	UGAGCUGAUGUAUGUGACG	920	8490	CGUCACAUACAUCAGCUCA	2672
rs2276881	8473	GAGCUGAUGUAUGUGACGC	921	8473	GAGCUGAUGUAUGUGACGC	921	8491	GCGUCACAUACAUCAGCUC	2673
rs2276881	8474	AGCUGAUGUAUGUGACGCU	922	8474	AGCUGAUGUAUGUGACGCU	922	8492	AGCGUCACAUACAUCAGCU	2674
rs2276881	8475	GCUGAUGUAUGUGACGCUG	923	8475	GCUGAUGUAUGUGACGCUG	923	8493	CAGCGUCACAUACAUCAGC	2675
rs2276881	8476	CUGAUGUAUGUGACGCUGA	924	8476	CUGAUGUAUGUGACGCUGA	924	8494	UCAGCGUCACAUACAUCAG	2676
rs2276881	8477	UGAUGUAUGUGACGCUGAC	925	8477	UGAUGUAUGUGACGCUGAC	925	8495	GUCAGCGUCACAUACAUCA	2677
rs2276881	8478	GAUGUAUGUGACGCUGACA	926	8478	GAUGUAUGUGACGCUGACA	926	8496	UGUCAGCGUCACAUACAUC	2678
rs2276881	8460	GCGCAACCAGUUUGAGCUA	927	8460	GCGCAACCAGUUUGAGCUA	927	8478	UAGCUCAAACUGGUUGCGC	2679
rs2276881	8461	CGCAACCAGUUUGAGCUAA	928	8461	CGCAACCAGUUUGAGCUAA	928	8479	UUAGCUCAAACUGGUUGCG	2680
rs2276881	8462	GCAACCAGUUUGAGCUAAU	929	8462	GCAACCAGUUUGAGCUAAU	929	8480	AUUAGCUCAAACUGGUUGC	2681
rs2276881	8463	CAACCAGUUUGAGCUAAUG	930	8463	CAACCAGUUUGAGCUAAUG	930	8481	CAUUAGCUCAAACUGGUUG	2682
rs2276881	8464	AACCAGUUUGAGCUAAUGU	931	8464	AACCAGUUUGAGCUAAUGU	931	8482	ACAUUAGCUCAAACUGGUU	2683
rs2276881	8465	ACCAGUUUGAGCUAAUGUA	932	8465	ACCAGUUUGAGCUAAUGUA	932	8483	UACAUUAGCUCAAACUGGU	2684

rs2276881	8466	CCAGUUUGAGCUAAUGUAU	933	8466	CCAGUUUGAGCUAAUGUAU	933	8484	AUACAUUAGCUCAAACUGG	2685
rs2276881	8467	CAGUUUGAGCUAAUGUAUG	934	8467	CAGUUUGAGCUAAUGUAUG	934	8485	CAUACAUUAGCUCAAACUG	2686
rs2276881	8468	AGUUUGAGCUAAUGUAUGU	935	8468	AGUUUGAGCUAAUGUAUGU	935	8486	ACAUACAUUAGCUCAAACU	2687
rs2276881	8469	GUUUGAGCUAAUGUAUGUG	936	8469	GUUUGAGCUAAUGUAUGUG	936	8487	CACAUACAUUAGCUCAAAC	2688
rs2276881	8470	UUUGAGCUAAUGUAUGUGA	937	8470	UUUGAGCUAAUGUAUGUGA	937	8488	UCACAUACAUUAGCUCAAA	2689
rs2276881	8471	UUGAGCUAAUGUAUGUGAC	938	8471	UUGAGCUAAUGUAUGUGAC	938	8489	GUCACAUACAUUAGCUCAA	2690
rs2276881	8472	UGAGCUAAUGUAUGUGACG	939	8472	UGAGCUAAUGUAUGUGACG	939	8490	CGUCACAUACAUUAGCUCA	2691
rs2276881	8473	GAGCUAAUGUAUGUGACGC	940	8473	GAGCUAAUGUAUGUGACGC	940	8491	GCGUCACAUACAUUAGCUC	2692
rs2276881	8474	AGCUAAUGUAUGUGACGCU	941	8474	AGCUAAUGUAUGUGACGCU	941	8492	AGCGUCACAUACAUUAGCU	2693
rs2276881	8475	GCUAAUGUAUGUGACGCUG	942	8475	GCUAAUGUAUGUGACGCUG	942	8493	CAGCGUCACAUACAUUAGC	2694
rs2276881	8476	CUAAUGUAUGUGACGCUGA	943	8476	CUAAUGUAUGUGACGCUGA	943	8494	UCAGCGUCACAUACAUUAG	2695
rs2276881	8477	UAAUGUAUGUGACGCUGAC	944	8477	UAAUGUAUGUGACGCUGAC	944	8495	GUCAGCGUCACAUACAUUA	2696
rs2276881	8478	AAUGUAUGUGACGCUGACA	945	8478	AAUGUAUGUGACGCUGACA	945	8496	UGUCAGCGUCACAUACAUU	2697
rs362272	8659	GUUGGAGCCCUGCACGGCG	946	8659	GUUGGAGCCCUGCACGGCG	946	8677	CGCCGUGCAGGGCUCCAAC	2698
rs362272	8660	UUGGAGCCCUGCACGGCGU	947	8660	UUGGAGCCCUGCACGGCGU	947	8678	ACGCCGUGCAGGGCUCCAA	2699
rs362272	8661	UGGAGCCCUGCACGGCGUC	948	8661	UGGAGCCCUGCACGGCGUC	948	8679	GACGCCGUGCAGGGCUCCA	2700
rs362272	8662	GGAGCCCUGCACGGCGUCC	949	8662	GGAGCCCUGCACGGCGUCC	949	8680	GGACGCCGUGCAGGGCUCC	2701
rs362272	8663	GAGCCCUGCACGGCGUCCU	950	8663	GAGCCCUGCACGGCGUCCU	950	8681	AGGACGCCGUGCAGGGCUC	2702
rs362272	8664	AGCCCUGCACGGCGUCCUC	951	8664	AGCCCUGCACGGCGUCCUC	951	8682	GAGGACGCCGUGCAGGGCU	2703
rs362272	8665	GCCCUGCACGGCGUCCUCU	952	8665	GCCCUGCACGGCGUCCUCU	952	8683	AGAGGACGCCGUGCAGGGC	2704
rs362272	8666	CCCUGCACGGCGUCCUCUA	953	8666	CCCUGCACGGCGUCCUCUA	953	8684	UAGAGGACGCCGUGCAGGG	2705
rs362272	8667	CCUGCACGGCGUCCUCUAU	954	8667	CCUGCACGGCGUCCUCUAU	954	8685	AUAGAGGACGCCGUGCAGG	2706
rs362272	8668	CUGCACGGCGUCCUCUAUG	955	8668	CUGCACGGCGUCCUCUAUG	955	8686	CAUAGAGGACGCCGUGCAG	2707
rs362272	8669	UGCACGGCGUCCUCUAUGU	956	8669	UGCACGGCGUCCUCUAUGU	956	8687	ACAUAGAGGACGCCGUGCA	2708
rs362272	8670	GCACGGCGUCCUCUAUGUG	957	8670	GCACGGCGUCCUCUAUGUG	957	8688	CACAUAGAGGACGCCGUGC	2709
rs362272	8671	CACGGCGUCCUCUAUGUGC	958	8671	CACGGCGUCCUCUAUGUGC	958	8689	GCACAUAGAGGACGCCGUG	2710
rs362272	8672	ACGGCGUCCUCUAUGUGCU	959	8672	ACGGCGUCCUCUAUGUGCU	959	8690	AGCACAUAGAGGACGCCGU	2711
rs362272	8673	CGGCGUCCUCUAUGUGCUG	960	8673	CGGCGUCCUCUAUGUGCUG	960	8691	CAGCACAUAGAGGACGCCG	2712
rs362272	8674	GGCGUCCUCUAUGUGCUGG	961	8674	GGCGUCCUCUAUGUGCUGG	961	8692	CCAGCACAUAGAGGACGCC	2713
rs362272	8675	GCGUCCUCUAUGUGCUGGA	962	8675	GCGUCCUCUAUGUGCUGGA	962	8693	UCCAGCACAUAGAGGACGC	2714
rs362272	8676	CGUCCUCUAUGUGCUGGAG	963	8676	CGUCCUCUAUGUGCUGGAG	963	8694	CUCCAGCACAUAGAGGACG	2715
rs362272	8677	GUCCUCUAUGUGCUGGAGU	964	8677	GUCCUCUAUGUGCUGGAGU	964	8695	ACUCCAGCACAUAGAGGAC	2716
rs362272	8659	GUUGGAGCCCUGCACGGCA	965	8659	GUUGGAGCCCUGCACGGCA	965	8677	UGCCGUGCAGGGCUCCAAC	2717
rs362272	8660	UUGGAGCCCUGCACGGCAU	966	8660	UUGGAGCCCUGCACGGCAU	966	8678	AUGCCGUGCAGGGCUCCAA	2718
rs362272	8661	UGGAGCCCUGCACGGCAUC	967	8661	UGGAGCCCUGCACGGCAUC	967	8679	GAUGCCGUGCAGGGCUCCA	2719
rs362272	8662	GGAGCCCUGCACGGCAUCC	968	8662	GGAGCCCUGCACGGCAUCC	968	8680	GGAUGCCGUGCAGGGCUCC	2720
rs362272	8663	GAGCCCUGCACGGCAUCCU	969	8663	GAGCCCUGCACGGCAUCCU	969	8681	AGGAUGCCGUGCAGGGCUC	2721
rs362272	8664	AGCCCUGCACGGCAUCCUC	970	8664	AGCCCUGCACGGCAUCCUC	970	8682	GAGGAUGCCGUGCAGGGCU	2722
rs362272	8665	GCCCUGCACGGCAUCCUCU	971	8665	GCCCUGCACGGCAUCCUCU	971	8683	AGAGGAUGCCGUGCAGGGC	2723

rs362272	8666	CCCUGCACGGCAUCCUCUA	972	8666	CCCUGCACGGCAUCCUCUA	972	8684	UAGAGGAUGCCGUGCAGGG	2724
rs362272	8667	CCUGCACGGCAUCCUCUAU	973	8667	CCUGCACGGCAUCCUCUAU	973	8685	AUAGAGGAUGCCGUGCAGG	2725
rs362272	8668	CUGCACGGCAUCCUCUAUG	974	8668	CUGCACGGCAUCCUCUAUG	974	8686	CAUAGAGGAUGCCGUGCAG	2726
rs362272	8669	UGCACGGCAUCCUCUAUGU	975	8669	UGCACGGCAUCCUCUAUGU	975	8687	ACAUAGAGGAUGCCGUGCA	2727
rs362272	8670	GCACGGCAUCCUCUAUGUG	976	8670	GCACGGCAUCCUCUAUGUG	976	8688	CACAUAGAGGAUGCCGUGC	2728
rs362272	8671	CACGGCAUCCUCUAUGUGC	977	8671	CACGGCAUCCUCUAUGUGC	977	8689	GCACAUAGAGGAUGCCGUG	2729
rs362272	8672	ACGGCAUCCUCUAUGUGCU	978	8672	ACGGCAUCCUCUAUGUGCU	978	8690	AGCACAUAGAGGAUGCCGU	2730
rs362272	8673	CGGCAUCCUCUAUGUGCUG	979	8673	CGGCAUCCUCUAUGUGCUG	979	8691	CAGCACAUAGAGGAUGCCG	2731
rs362272	8674	GGCAUCCUCUAUGUGCUGG	980	8674	GGCAUCCUCUAUGUGCUGG	980	8692	CCAGCACAUAGAGGAUGCC	2732
rs362272	8675	GCAUCCUCUAUGUGCUGGA	981	8675	GCAUCCUCUAUGUGCUGGA	981	8693	UCCAGCACAUAGAGGAUGC	2733
rs362272	8676	CAUCCUCUAUGUGCUGGAG	982	8676	CAUCCUCUAUGUGCUGGAG	982	8694	CUCCAGCACAUAGAGGAUG	2734
rs362272	8677	AUCCUCUAUGUGCUGGAGU	983	8677	AUCCUCUAUGUGCUGGAGU	983	8695	ACUCCAGCACAUAGAGGAU	2735
rs3025807	9136	UCAGACCCUAAUCCUGCAG	984	9136	UCAGACCCUAAUCCUGCAG	984	9154	CUGCAGGAUUAGGGUCUGA	2736
rs3025807	9137	CAGACCCUAAUCCUGCAGC	985	9137	CAGACCCUAAUCCUGCAGC	985	9155	GCUGCAGGAUUAGGGUCUG	2737
rs3025807	9138	AGACCCUAAUCCUGCAGCC	986	9138	AGACCCUAAUCCUGCAGCC	986	9156	GGCUGCAGGAUUAGGGUCU	2738
rs3025807	9139	GACCCUAAUCCUGCAGCCC	987	9139	GACCCUAAUCCUGCAGCCC	987	9157	GGGCUGCAGGAUUAGGGUC	2739
rs3025807	9140	ACCCUAAUCCUGCAGCCCC	988	9140	ACCCUAAUCCUGCAGCCCC	988	9158	GGGGCUGCAGGAUUAGGGU	2740
rs3025807	9141	CCCUAAUCCUGCAGCCCCC	989	9141	CCCUAAUCCUGCAGCCCCC	989	9159	GGGGGCUGCAGGAUUAGGG	2741
rs3025807	9142	CCUAAUCCUGCAGCCCCCG	990	9142	CCUAAUCCUGCAGCCCCCG	990	9160	CGGGGGCUGCAGGAUUAGG	2742
rs3025807	9143	CUAAUCCUGCAGCCCCCGA	991	9143	CUAAUCCUGCAGCCCCCGA	991	9161	UCGGGGGCUGCAGGAUUAG	2743
rs3025807	9144	UAAUCCUGCAGCCCCCGAC	992	9144	UAAUCCUGCAGCCCCCGAC	992	9162	GUCGGGGGCUGCAGGAUUA	2744
rs3025807	9145	AAUCCUGCAGCCCCCGACA	993	9145	AAUCCUGCAGCCCCCGACA	993	9163	UGUCGGGGGCUGCAGGAUU	2745
rs3025807	9146	AUCCUGCAGCCCCCGACAG	994	9146	AUCCUGCAGCCCCCGACAG	994	9164	CUGUCGGGGGCUGCAGGAU	2746
rs3025807	9147	UCCUGCAGCCCCCGACAGC	995	9147	UCCUGCAGCCCCCGACAGC	995	9165	GCUGUCGGGGGCUGCAGGA	2747
rs3025807	9148	CCUGCAGCCCCCGACAGCG	996	9148	CCUGCAGCCCCCGACAGCG	996	9166	CGCUGUCGGGGGCUGCAGG	2748
rs3025807	9149	CUGCAGCCCCCGACAGCGA	997	9149	CUGCAGCCCCCGACAGCGA	997	9167	UCGCUGUCGGGGGCUGCAG	2749
rs3025807	9150	UGCAGCCCCCGACAGCGAG	998	9150	UGCAGCCCCCGACAGCGAG	998	9168	CUCGCUGUCGGGGGCUGCA	2750
rs3025807	9151	GCAGCCCCCGACAGCGAGU	999	9151	GCAGCCCCCGACAGCGAGU	999	9169	ACUCGCUGUCGGGGGCUGC	2751
rs3025807	9152	CAGCCCCCGACAGCGAGUC	1000	9152	CAGCCCCCGACAGCGAGUC	1000	9170	GACUCGCUGUCGGGGGCUG	2752
rs3025807	9153	AGCCCCCGACAGCGAGUCA	1001	9153	AGCCCCCGACAGCGAGUCA	1001	9171	UGACUCGCUGUCGGGGGCU	2753
rs3025807	9154	GCCCCCGACAGCGAGUCAG	1002	9154	GCCCCCGACAGCGAGUCAG	1002	9172	CUGACUCGCUGUCGGGGGC	2754
rs3025807	9136	UCAGACCCUAAUCCUGCAT	1003	9136	UCAGACCCUAAUCCUGCAT	1003	9154	AUGCAGGAUUAGGGUCUGA	2755
rs3025807	9137	CAGACCCUAAUCCUGCATC	1004	9137	CAGACCCUAAUCCUGCATC	1004	9155	GAUGCAGGAUUAGGGUCUG	2756
rs3025807	9138	AGACCCUAAUCCUGCATCC	1005	9138	AGACCCUAAUCCUGCATCC	1005	9156	GGAUGCAGGAUUAGGGUCU	2757
rs3025807	9139	GACCCUAAUCCUGCATCCC	1006	9139	GACCCUAAUCCUGCATCCC	1006	9157	GGGAUGCAGGAUUAGGGUC	2758
rs3025807	9140	ACCCUAAUCCUGCATCCCC	1007	9140	ACCCUAAUCCUGCATCCCC	1007	9158	GGGGAUGCAGGAUUAGGGU	2759
rs3025807	9141	CCCUAAUCCUGCATCCCCC	1008	9141	CCCUAAUCCUGCATCCCCC	1008	9159	GGGGGAUGCAGGAUUAGGG	2760
rs3025807	9142	CCUAAUCCUGCATCCCCCG	1009	9142	CCUAAUCCUGCATCCCCCG	1009	9160	CGGGGGAUGCAGGAUUAGG	2761
rs3025807	9143	CUAAUCCUGCATCCCCCGA	1010	9143	CUAAUCCUGCATCCCCCGA	1010	9161	UCGGGGGAUGCAGGAUUAG	2762

rs3025807	9144	UAAUCCUGCATCCCCCGAC	1011	9144	UAAUCCUGCATCCCCCGAC	1011	9162	GUCGGGGGAUGCAGGAUUA	2763
rs3025807	9145	AAUCCUGCATCCCCCGACA	1012	9145	AAUCCUGCATCCCCCGACA	1012	9163	UGUCGGGGGAUGCAGGAUU	2764
rs3025807	9146	AUCCUGCATCCCCCGACAG	1013	9146	AUCCUGCATCCCCCGACAG	1013	9164	CUGUCGGGGGAUGCAGGAU	2765
rs3025807	9147	UCCUGCATCCCCCGACAGC	1014	9147	UCCUGCATCCCCCGACAGC	1014	9165	GCUGUCGGGGGAUGCAGGA	2766
rs3025807	9148	CCUGCATCCCCCGACAGCG	1015	9148	CCUGCATCCCCCGACAGCG	1015	9166	CGCUGUCGGGGGAUGCAGG	2767
rs3025807	9149	CUGCATCCCCCGACAGCGA	1016	9149	CUGCATCCCCCGACAGCGA	1016	9167	UCGCUGUCGGGGGAUGCAG	2768
rs3025807	9150	UGCATCCCCCGACAGCGAG	1017	9150	UGCATCCCCCGACAGCGAG	1017	9168	CUCGCUGUCGGGGGAUGCA	2769
rs3025807	9151	GCATCCCCCGACAGCGAGU	1018	9151	GCATCCCCCGACAGCGAGU	1018	9169	ACUCGCUGUCGGGGGAUGC	2770
rs3025807	9152	CATCCCCCGACAGCGAGUC	1019	9152	CATCCCCCGACAGCGAGUC	1019	9170	GACUCGCUGUCGGGGGAUG	2771
rs3025807	9153	ATCCCCCGACAGCGAGUCA	1020	9153	ATCCCCCGACAGCGAGUCA	1020	9171	UGACUCGCUGUCGGGGGAU	2772
rs3025807	9154	TCCCCCGACAGCGAGUCAG	1021	9154	TCCCCCGACAGCGAGUCAG	1021	9172	CUGACUCGCUGUCGGGGGA	2773
rs362308	9681	AGCCCCAGGAAGCCCAUAU	1022	9681	AGCCCCAGGAAGCCCAUAU	1022	9699	AUAUGGGCUUCCUGGGGCU	2774
rs362308	9682	GCCCCAGGAAGCCCAUAUC	1023	9682	GCCCCAGGAAGCCCAUAUC	1023	9700	GAUAUGGGCUUCCUGGGGC	2775
rs362308	9683	CCCCAGGAAGCCCAUAUCA	1024	9683	CCCCAGGAAGCCCAUAUCA	1024	9701	UGAUAUGGGCUUCCUGGGG	2776
rs362308	9684	CCCAGGAAGCCCAUAUCAC	1025	9684	CCCAGGAAGCCCAUAUCAC	1025	9702	GUGAUAUGGGCUUCCUGGG	2777
rs362308	9685	CCAGGAAGCCCAUAUCACC	1026	9685	CCAGGAAGCCCAUAUCACC	1026	9703	GGUGAUAUGGGCUUCCUGG	2778
rs362308	9686	CAGGAAGCCCAUAUCACCG	1027	9686	CAGGAAGCCCAUAUCACCG	1027	9704	CGGUGAUAUGGGCUUCCUG	2779
rs362308	9687	AGGAAGCCCAUAUCACCGG	1028	9687	AGGAAGCCCAUAUCACCGG	1028	9705	CCGGUGAUAUGGGCUUCCU	2780
rs362308	9688	GGAAGCCCAUAUCACCGGC	1029	9688	GGAAGCCCAUAUCACCGGC	1029	9706	GCCGGUGAUAUGGGCUUCC	2781
rs362308	9689	GAAGCCCAUAUCACCGGCU	1030	9689	GAAGCCCAUAUCACCGGCU	1030	9707	AGCCGGUGAUAUGGGCUUC	2782
rs362308	9690	AAGCCCAUAUCACCGGCUG	1031	9690	AAGCCCAUAUCACCGGCUG	1031	9708	CAGCCGGUGAUAUGGGCUU	2783
rs362308	9691	AGCCCAUAUCACCGGCUGC	1032	9691	AGCCCAUAUCACCGGCUGC	1032	9709	GCAGCCGGUGAUAUGGGCU	2784
rs362308	9692	GCCCAUAUCACCGGCUGCU	1033	9692	GCCCAUAUCACCGGCUGCU	1033	9710	AGCAGCCGGUGAUAUGGGC	2785
rs362308	9693	CCCAUAUCACCGGCUGCUG	1034	9693	CCCAUAUCACCGGCUGCUG	1034	9711	CAGCAGCCGGUGAUAUGGG	2786
rs362308	9694	CCAUAUCACCGGCUGCUGA	1035	9694	CCAUAUCACCGGCUGCUGA	1035	9712	UCAGCAGCCGGUGAUAUGG	2787
rs362308	9695	CAUAUCACCGGCUGCUGAC	1036	9695	CAUAUCACCGGCUGCUGAC	1036	9713	GUCAGCAGCCGGUGAUAUG	2788
rs362308	9696	AUAUCACCGGCUGCUGACU	1037	9696	AUAUCACCGGCUGCUGACU	1037	9714	AGUCAGCAGCCGGUGAUAU	2789
rs362308	9697	UAUCACCGGCUGCUGACUU	1038	9697	UAUCACCGGCUGCUGACUU	1038	9715	AAGUCAGCAGCCGGUGAUA	2790
rs362308	9698	AUCACCGGCUGCUGACUUG	1039	9698	AUCACCGGCUGCUGACUUG	1039	9716	CAAGUCAGCAGCCGGUGAU	2791
rs362308	9699	UCACCGGCUGCUGACUUGU	1040	9699	UCACCGGCUGCUGACUUGU	1040	9717	ACAAGUCAGCAGCCGGUGA	2792
rs362308	9681	AGCCCCAGGAAGCCCAUAC	1041	9681	AGCCCCAGGAAGCCCAUAC	1041	9699	GUAUGGGCUUCCUGGGGCU	2793
rs362308	9682	GCCCCAGGAAGCCCAUACC	1042	9682	GCCCCAGGAAGCCCAUACC	1042	9700	GGUAUGGGCUUCCUGGGGC	2794
rs362308	9683	CCCCAGGAAGCCCAUACCA	1043	9683	CCCCAGGAAGCCCAUACCA	1043	9701	UGGUAUGGGCUUCCUGGGG	2795
rs362308	9684	CCCAGGAAGCCCAUACCAC	1044	9684	CCCAGGAAGCCCAUACCAC	1044	9702	GUGGUAUGGGCUUCCUGGG	2796
rs362308	9685	CCAGGAAGCCCAUACCACC	1045	9685	CCAGGAAGCCCAUACCACC	1045	9703	GGUGGUAUGGGCUUCCUGG	2797
rs362308	9686	CAGGAAGCCCAUACCACCG	1046	9686	CAGGAAGCCCAUACCACCG	1046	9704	CGGUGGUAUGGGCUUCCUG	2798
rs362308	9687	AGGAAGCCCAUACCACCGG	1047	9687	AGGAAGCCCAUACCACCGG	1047	9705	CCGGUGGUAUGGGCUUCCU	2799
rs362308	9688	GGAAGCCCAUACCACCGGC	1048	9688	GGAAGCCCAUACCACCGGC	1048	9706	GCCGGUGGUAUGGGCUUCC	2800
rs362308	9689	GAAGCCCAUACCACCGGCU	1049	9689	GAAGCCCAUACCACCGGCU	1049	9707	AGCCGGUGGUAUGGGCUUC	2801

rs362308	9690	AAGCCCAUACCACCGGCUG	1050	9690	AAGCCCAUACCACCGGCUG	1050	9708	CAGCCGGUGGUAUGGGCUU	2802
rs362308	9691	AGCCCAUACCACCGGCUGC	1051	9691	AGCCCAUACCACCGGCUGC	1051	9709	GCAGCCGGUGGUAUGGGCU	2803
rs362308	9692	GCCCAUACCACCGGCUGCU	1052	9692	GCCCAUACCACCGGCUGCU	1052	9710	AGCAGCCGGUGGUAUGGGC	2804
rs362308	9693	CCCAUACCACCGGCUGCUG	1053	9693	CCCAUACCACCGGCUGCUG	1053	9711	CAGCAGCCGGUGGUAUGGG	2805
rs362308	9694	CCAUACCACCGGCUGCUGA	1054	9694	CCAUACCACCGGCUGCUGA	1054	9712	UCAGCAGCCGGUGGUAUGG	2806
rs362308	9695	CAUACCACCGGCUGCUGAC	1055	9695	CAUACCACCGGCUGCUGAC	1055	9713	GUCAGCAGCCGGUGGUAUG	2807
rs362308	9696	AUACCACCGGCUGCUGACU	1056	9696	AUACCACCGGCUGCUGACU	1056	9714	AGUCAGCAGCCGGUGGUAU	2808
rs362308	9697	UACCACCGGCUGCUGACUU	1057	9697	UACCACCGGCUGCUGACUU	1057	9715	AAGUCAGCAGCCGGUGGUA	2809
rs362308	9698	ACCACCGGCUGCUGACUUG	1058	9698	ACCACCGGCUGCUGACUUG	1058	9716	CAAGUCAGCAGCCGGUGGU	2810
rs362308	9699	CCACCGGCUGCUGACUUGU	1059	9699	CCACCGGCUGCUGACUUGU	1059	9717	ACAAGUCAGCAGCCGGUGG	2811
rs362307	9791	GGAGCCUUUGGAAGUCUGU	1060	9791	GGAGCCUUUGGAAGUCUGU	1060	9809	ACAGACUUCCAAAGGCUCC	2812
rs362307	9792	GAGCCUUUGGAAGUCUGUG	1061	9792	GAGCCUUUGGAAGUCUGUG	1061	9810	CACAGACUUCCAAAGGCUC	2813
rs362307	9793	AGCCUUUGGAAGUCUGUGC	1062	9793	AGCCUUUGGAAGUCUGUGC	1062	9811	GCACAGACUUCCAAAGGCU	2814
rs362307	9794	GCCUUUGGAAGUCUGUGCC	1063	9794	GCCUUUGGAAGUCUGUGCC	1063	9812	GGCACAGACUUCCAAAGGC	2815
rs362307	9795	CCUUUGGAAGUCUGUGCCC	1064	9795	CCUUUGGAAGUCUGUGCCC	1064	9813	GGGCACAGACUUCCAAAGG	2816
rs362307	9796	CUUUGGAAGUCUGUGCCCU	1065	9796	CUUUGGAAGUCUGUGCCCU	1065	9814	AGGGCACAGACUUCCAAAG	2817
rs362307	9797	UUUGGAAGUCUGUGCCCUU	1066	9797	UUUGGAAGUCUGUGCCCUU	1066	9815	AAGGGCACAGACUUCCAAA	2818
rs362307	9798	UUGGAAGUCUGUGCCCUUG	1067	9798	UUGGAAGUCUGUGCCCUUG	1067	9816	CAAGGGCACAGACUUCCAA	2819
rs362307	9799	UGGAAGUCUGUGCCCUUGU	1068	9799	UGGAAGUCUGUGCCCUUGU	1068	9817	ACAAGGGCACAGACUUCCA	2820
rs362307	9800	GGAAGUCUGUGCCCUUGUG	1069	9800	GGAAGUCUGUGCCCUUGUG	1069	9818	CACAAGGGCACAGACUUCC	2821
rs362307	9801	GAAGUCUGUGCCCUUGUGC	1070	9801	GAAGUCUGUGCCCUUGUGC	1070	9819	GCACAAGGGCACAGACUUC	2822
rs362307	9802	AAGUCUGUGCCCUUGUGCC	1071	9802	AAGUCUGUGCCCUUGUGCC	1071	9820	GGCACAAGGGCACAGACUU	2823
rs362307	9803	AGUCUGUGCCCUUGUGCCC	1072	9803	AGUCUGUGCCCUUGUGCCC	1072	9821	GGGCACAAGGGCACAGACU	2824
rs362307	9804	GUCUGUGCCCUUGUGCCCU	1073	9804	GUCUGUGCCCUUGUGCCCU	1073	9822	AGGGCACAAGGGCACAGAC	2825
rs362307	9805	UCUGUGCCCUUGUGCCCUG	1074	9805	UCUGUGCCCUUGUGCCCUG	1074	9823	CAGGGCACAAGGGCACAGA	2826
rs362307	9806	CUGUGCCCUUGUGCCCUGC	1075	9806	CUGUGCCCUUGUGCCCUGC	1075	9824	GCAGGGCACAAGGGCACAG	2827
rs362307	9807	UGUGCCCUUGUGCCCUGCC	1076	9807	UGUGCCCUUGUGCCCUGCC	1076	9825	GGCAGGGCACAAGGGCACA	2828
rs362307	9808	GUGCCCUUGUGCCCUGCCU	1077	9808	GUGCCCUUGUGCCCUGCCU	1077	9826	AGGCAGGGCACAAGGGCAC	2829
rs362307	9809	UGCCCUUGUGCCCUGCCUC	1078	9809	UGCCCUUGUGCCCUGCCUC	1078	9827	GAGGCAGGGCACAAGGGCA	2830
rs362307	9791	GGAGCCUUUGGAAGUCUGC	1079	9791	GGAGCCUUUGGAAGUCUGC	1079	9809	GCAGACUUCCAAAGGCUCC	2831
rs362307	9792	GAGCCUUUGGAAGUCUGCG	1080	9792	GAGCCUUUGGAAGUCUGCG	1080	9810	CGCAGACUUCCAAAGGCUC	2832
rs362307	9793	AGCCUUUGGAAGUCUGCGC	1081	9793	AGCCUUUGGAAGUCUGCGC	1081	9811	GCGCAGACUUCCAAAGGCU	2833
rs362307	9794	GCCUUUGGAAGUCUGCGCC	1082	9794	GCCUUUGGAAGUCUGCGCC	1082	9812	GGCGCAGACUUCCAAAGGC	2834
rs362307	9795	CCUUUGGAAGUCUGCGCCC	1083	9795	CCUUUGGAAGUCUGCGCCC	1083	9813	GGGCGCAGACUUCCAAAGG	2835
rs362307	9796	CUUUGGAAGUCUGCGCCCU	1084	9796	CUUUGGAAGUCUGCGCCCU	1084	9814	AGGGCGCAGACUUCCAAAG	2836
rs362307	9797	UUUGGAAGUCUGCGCCCUU	1085	9797	UUUGGAAGUCUGCGCCCUU	1085	9815	AAGGGCGCAGACUUCCAAA	2837
rs362307	9798	UUGGAAGUCUGCGCCCUUG	1086	9798	UUGGAAGUCUGCGCCCUUG	1086	9816	CAAGGGCGCAGACUUCCAA	2838
rs362307	9799	UGGAAGUCUGCGCCCUUGU	1087	9799	UGGAAGUCUGCGCCCUUGU	1087	9817	ACAAGGGCGCAGACUUCCA	2839
rs362307	9800	GGAAGUCUGCGCCCUUGUG	1088	9800	GGAAGUCUGCGCCCUUGUG	1088	9818	CACAAGGGCGCAGACUUCC	2840

rs362307	9801	GAAGUCUGCGCCCUUGUGC	1089	9801	GAAGUCUGCGCCCUUGUGC	1089	9819	GCACAAGGGCGCAGACUUC	2841
rs362307	9802	AAGUCUGCGCCCUUGUGCC	1090	9802	AAGUCUGCGCCCUUGUGCC	1090	9820	GGCACAAGGGCGCAGACUU	2842
rs362307	9803	AGUCUGCGCCCUUGUGCCC	1091	9803	AGUCUGCGCCCUUGUGCCC	1091	9821	GGGCACAAGGGCGCAGACU	2843
rs362307	9804	GUCUGCGCCCUUGUGCCCU	1092	9804	GUCUGCGCCCUUGUGCCCU	1092	9822	AGGGCACAAGGGCGCAGAC	2844
rs362307	9805	UCUGCGCCCUUGUGCCCUG	1093	9805	UCUGCGCCCUUGUGCCCUG	1093	9823	CAGGGCACAAGGGCGCAGA	2845
rs362307	9806	CUGCGCCCUUGUGCCCUGC	1094	9806	CUGCGCCCUUGUGCCCUGC	1094	9824	GCAGGGCACAAGGGCGCAG	2846
rs362307	9807	UGCGCCCUUGUGCCCUGCC	1095	9807	UGCGCCCUUGUGCCCUGCC	1095	9825	GGCAGGGCACAAGGGCGCA	2847
rs362307	9808	GCGCCCUUGUGCCCUGCCU	1096	9808	GCGCCCUUGUGCCCUGCCU	1096	9826	AGGCAGGGCACAAGGGCGC	2848
rs362307	9809	CGCCCUUGUGCCCUGCCUC	1097	9809	CGCCCUUGUGCCCUGCCUC	1097	9827	GAGGCAGGGCACAAGGGCG	2849
rs362306	10046	GCUGGUUGUUGCCAGGUUG	1098	10046	GCUGGUUGUUGCCAGGUUG	1098	10064	CAACCUGGCAACAACCAGC	2850
rs362306	10047	CUGGUUGUUGCCAGGUUGC	1099	10047	CUGGUUGUUGCCAGGUUGC	1099	10065	GCAACCUGGCAACAACCAG	2851
rs362306	10048	UGGUUGUUGCCAGGUUGCA	1100	10048	UGGUUGUUGCCAGGUUGCA	1100	10066	UGCAACCUGGCAACAACCA	2852
rs362306	10049	GGUUGUUGCCAGGUUGCAG	1101	10049	GGUUGUUGCCAGGUUGCAG	1101	10067	CUGCAACCUGGCAACAACC	2853
rs362306	10050	GUUGUUGCCAGGUUGCAGC	1102	10050	GUUGUUGCCAGGUUGCAGC	1102	10068	GCUGCAACCUGGCAACAAC	2854
rs362306	10051	UUGUUGCCAGGUUGCAGCU	1103	10051	UUGUUGCCAGGUUGCAGCU	1103	10069	AGCUGCAACCUGGCAACAA	2855
rs362306	10052	UGUUGCCAGGUUGCAGCUG	1104	10052	UGUUGCCAGGUUGCAGCUG	1104	10070	CAGCUGCAACCUGGCAACA	2856
rs362306	10053	GUUGCCAGGUUGCAGCUGC	1105	10053	GUUGCCAGGUUGCAGCUGC	1105	10071	GCAGCUGCAACCUGGCAAC	2857
rs362306	10054	UUGCCAGGUUGCAGCUGCU	1106	10054	UUGCCAGGUUGCAGCUGCU	1106	10072	AGCAGCUGCAACCUGGCAA	2858
rs362306	10055	UGCCAGGUUGCAGCUGCUC	1107	10055	UGCCAGGUUGCAGCUGCUC	1107	10073	GAGCAGCUGCAACCUGGCA	2859
rs362306	10056	GCCAGGUUGCAGCUGCUCU	1108	10056	GCCAGGUUGCAGCUGCUCU	1108	10074	AGAGCAGCUGCAACCUGGC	2860
rs362306	10057	CCAGGUUGCAGCUGCUCUU	1109	10057	CCAGGUUGCAGCUGCUCUU	1109	10075	AAGAGCAGCUGCAACCUGG	2861
rs362306	10058	CAGGUUGCAGCUGCUCUUG	1110	10058	CAGGUUGCAGCUGCUCUUG	1110	10076	CAAGAGCAGCUGCAACCUG	2862
rs362306	10059	AGGUUGCAGCUGCUCUUGC	1111	10059	AGGUUGCAGCUGCUCUUGC	1111	10077	GCAAGAGCAGCUGCAACCU	2863
rs362306	10060	GGUUGCAGCUGCUCUUGCA	1112	10060	GGUUGCAGCUGCUCUUGCA	1112	10078	UGCAAGAGCAGCUGCAACC	2864
rs362306	10061	GUUGCAGCUGCUCUUGCAU	1113	10061	GUUGCAGCUGCUCUUGCAU	1113	10079	AUGCAAGAGCAGCUGCAAC	2865
rs362306	10062	UUGCAGCUGCUCUUGCAUC	1114	10062	UUGCAGCUGCUCUUGCAUC	1114	10080	GAUGCAAGAGCAGCUGCAA	2866
rs362306	10063	UGCAGCUGCUCUUGCAUCU	1115	10063	UGCAGCUGCUCUUGCAUCU	1115	10081	AGAUGCAAGAGCAGCUGCA	2867
rs362306	10064	GCAGCUGCUCUUGCAUCUG	1116	10064	GCAGCUGCUCUUGCAUCUG	1116	10082	CAGAUGCAAGAGCAGCUGC	2868
rs362306	10046	GCUGGUUGUUGCCAGGUUA	1117	10046	GCUGGUUGUUGCCAGGUUA	1117	10064	UAACCUGGCAACAACCAGC	2869
rs362306	10047	CUGGUUGUUGCCAGGUUAC	1118	10047	CUGGUUGUUGCCAGGUUAC	1118	10065	GUAACCUGGCAACAACCAG	2870
rs362306	10048	UGGUUGUUGCCAGGUUACA	1119	10048	UGGUUGUUGCCAGGUUACA	1119	10066	UGUAACCUGGCAACAACCA	2871
rs362306	10049	GGUUGUUGCCAGGUUACAG	1120	10049	GGUUGUUGCCAGGUUACAG	1120	10067	CUGUAACCUGGCAACAACC	2872
rs362306	10050	GUUGUUGCCAGGUUACAGC	1121	10050	GUUGUUGCCAGGUUACAGC	1121	10068	GCUGUAACCUGGCAACAAC	2873
rs362306	10051	UUGUUGCCAGGUUACAGCU	1122	10051	UUGUUGCCAGGUUACAGCU	1122	10069	AGCUGUAACCUGGCAACAA	2874
rs362306	10052	UGUUGCCAGGUUACAGCUG	1123	10052	UGUUGCCAGGUUACAGCUG	1123	10070	CAGCUGUAACCUGGCAACA	2875
rs362306	10053	GUUGCCAGGUUACAGCUGC	1124	10053	GUUGCCAGGUUACAGCUGC	1124	10071	GCAGCUGUAACCUGGCAAC	2876
rs362306	10054	UUGCCAGGUUACAGCUGCU	1125	10054	UUGCCAGGUUACAGCUGCU	1125	10072	AGCAGCUGUAACCUGGCAA	2877
rs362306	10055	UGCCAGGUUACAGCUGCUC	1126	10055	UGCCAGGUUACAGCUGCUC	1126	10073	GAGCAGCUGUAACCUGGCA	2878
rs362306	10056	GCCAGGUUACAGCUGCUCU	1127	10056	GCCAGGUUACAGCUGCUCU	1127	10074	AGAGCAGCUGUAACCUGGC	2879

rs362306	10057	CCAGGUUACAGCUGCUCUU	1128	10057	CCAGGUUACAGCUGCUCUU	1128	10075	AAGAGCAGCUGUAACCUGG	2880
rs362306	10058	CAGGUUACAGCUGCUCUUG	1129	10058	CAGGUUACAGCUGCUCUUG	1129	10076	CAAGAGCAGCUGUAACCUG	2881
rs362306	10059	AGGUUACAGCUGCUCUUGC	1130	10059	AGGUUACAGCUGCUCUUGC	1130	10077	GCAAGAGCAGCUGUAACCU	2882
rs362306	10060	GGUUACAGCUGCUCUUGCA	1131	10060	GGUUACAGCUGCUCUUGCA	1131	10078	UGCAAGAGCAGCUGUAACC	2883
rs362306	10061	GUUACAGCUGCUCUUGCAU	1132	10061	GUUACAGCUGCUCUUGCAU	1132	10079	AUGCAAGAGCAGCUGUAAC	2884
rs362306	10062	UUACAGCUGCUCUUGCAUC	1133	10062	UUACAGCUGCUCUUGCAUC	1133	10080	GAUGCAAGAGCAGCUGUAA	2885
rs362306	10063	UACAGCUGCUCUUGCAUCU	1134	10063	UACAGCUGCUCUUGCAUCU	1134	10081	AGAUGCAAGAGCAGCUGUA	2886
rs362306	10064	ACAGCUGCUCUUGCAUCUG	1135	10064	ACAGCUGCUCUUGCAUCUG	1135	10082	CAGAUGCAAGAGCAGCUGU	2887
rs362268	10094	CUCCCUCCUGCAGGCUGGC	1136	10094	CUCCCUCCUGCAGGCUGGC	1136	10112	GCCAGCCUGCAGGAGGGAG	2888
rs362268	10095	UCCCUCCUGCAGGCUGGCU	1137	10095	UCCCUCCUGCAGGCUGGCU	1137	10113	AGCCAGCCUGCAGGAGGGA	2889
rs362268	10096	CCCUCCUGCAGGCUGGCUG	1138	10096	CCCUCCUGCAGGCUGGCUG	1138	10114	CAGCCAGCCUGCAGGAGGG	2890
rs362268	10097	CCUCCUGCAGGCUGGCUGU	1139	10097	CCUCCUGCAGGCUGGCUGU	1139	10115	ACAGCCAGCCUGCAGGAGG	2891
rs362268	10098	CUCCUGCAGGCUGGCUGUU	1140	10098	CUCCUGCAGGCUGGCUGUU	1140	10116	AACAGCCAGCCUGCAGGAG	2892
rs362268	10099	UCCUGCAGGCUGGCUGUUG	1141	10099	UCCUGCAGGCUGGCUGUUG	1141	10117	CAACAGCCAGCCUGCAGGA	2893
rs362268	10100	CCUGCAGGCUGGCUGUUGG	1142	10100	CCUGCAGGCUGGCUGUUGG	1142	10118	CCAACAGCCAGCCUGCAGG	2894
rs362268	10101	CUGCAGGCUGGCUGUUGGC	1143	10101	CUGCAGGCUGGCUGUUGGC	1143	10119	GCCAACAGCCAGCCUGCAG	2895
rs362268	10102	UGCAGGCUGGCUGUUGGCC	1144	10102	UGCAGGCUGGCUGUUGGCC	1144	10120	GGCCAACAGCCAGCCUGCA	2896
rs362268	10103	GCAGGCUGGCUGUUGGCCC	1145	10103	GCAGGCUGGCUGUUGGCCC	1145	10121	GGGCCAACAGCCAGCCUGC	2897
rs362268	10104	CAGGCUGGCUGUUGGCCCC	1146	10104	CAGGCUGGCUGUUGGCCCC	1146	10122	GGGGCCAACAGCCAGCCUG	2898
rs362268	10105	AGGCUGGCUGUUGGCCCCU	1147	10105	AGGCUGGCUGUUGGCCCCU	1147	10123	AGGGGCCAACAGCCAGCCU	2899
rs362268	10106	GGCUGGCUGUUGGCCCCUC	1148	10106	GGCUGGCUGUUGGCCCCUC	1148	10124	GAGGGGCCAACAGCCAGCC	2900
rs362268	10107	GCUGGCUGUUGGCCCCUCU	1149	10107	GCUGGCUGUUGGCCCCUCU	1149	10125	AGAGGGGCCAACAGCCAGC	2901
rs362268	10108	CUGGCUGUUGGCCCCUCUG	1150	10108	CUGGCUGUUGGCCCCUCUG	1150	10126	CAGAGGGGCCAACAGCCAG	2902
rs362268	10109	UGGCUGUUGGCCCCUCUGC	1151	10109	UGGCUGUUGGCCCCUCUGC	1151	10127	GCAGAGGGGCCAACAGCCA	2903
rs362268	10110	GGCUGUUGGCCCCUCUGCU	1152	10110	GGCUGUUGGCCCCUCUGCU	1152	10128	AGCAGAGGGGCCAACAGCC	2904
rs362268	10111	GCUGUUGGCCCCUCUGCUG	1153	10111	GCUGUUGGCCCCUCUGCUG	1153	10129	CAGCAGAGGGGCCAACAGC	2905
rs362268	10112	CUGUUGGCCCCUCUGCUGU	1154	10112	CUGUUGGCCCCUCUGCUGU	1154	10130	ACAGCAGAGGGGCCAACAG	2906
rs362268	10094	CUCCCUCCUGCAGGCUGGG	1155	10094	CUCCCUCCUGCAGGCUGGG	1155	10112	CCCAGCCUGCAGGAGGGAG	2907
rs362268	10095	UCCCUCCUGCAGGCUGGGU	1156	10095	UCCCUCCUGCAGGCUGGGU	1156	10113	ACCCAGCCUGCAGGAGGGA	2908
rs362268	10096	CCCUCCUGCAGGCUGGGUG	1157	10096	CCCUCCUGCAGGCUGGGUG	1157	10114	CACCCAGCCUGCAGGAGGG	2909
rs362268	10097	CCUCCUGCAGGCUGGGUGU	1158	10097	CCUCCUGCAGGCUGGGUGU	1158	10115	ACACCCAGCCUGCAGGAGG	2910
rs362268	10098	CUCCUGCAGGCUGGGUGUU	1159	10098	CUCCUGCAGGCUGGGUGUU	1159	10116	AACACCCAGCCUGCAGGAG	2911
rs362268	10099	UCCUGCAGGCUGGGUGUUG	1160	10099	UCCUGCAGGCUGGGUGUUG	1160	10117	CAACACCCAGCCUGCAGGA	2912
rs362268	10100	CCUGCAGGCUGGGUGUUGG	1161	10100	CCUGCAGGCUGGGUGUUGG	1161	10118	CCAACACCCAGCCUGCAGG	2913
rs362268	10101	CUGCAGGCUGGGUGUUGGC	1162	10101	CUGCAGGCUGGGUGUUGGC	1162	10119	GCCAACACCCAGCCUGCAG	2914
rs362268	10102	UGCAGGCUGGGUGUUGGCC	1163	10102	UGCAGGCUGGGUGUUGGCC	1163	10120	GGCCAACACCCAGCCUGCA	2915
rs362268	10103	GCAGGCUGGGUGUUGGCCC	1164	10103	GCAGGCUGGGUGUUGGCCC	1164	10121	GGGCCAACACCCAGCCUGC	2916
rs362268	10104	CAGGCUGGGUGUUGGCCCC	1165	10104	CAGGCUGGGUGUUGGCCCC	1165	10122	GGGGCCAACACCCAGCCUG	2917
rs362268	10105	AGGCUGGGUGUUGGCCCCU	1166	10105	AGGCUGGGUGUUGGCCCCU	1166	10123	AGGGGCCAACACCCAGCCU	2918

rs362305	10113	UGUUGGCCCCUCUGCUGUC	1167	10113	UGUUGGCCCCUCUGCUGUC	1167	10131	GACAGCAGAGGGGCCAACA	2919
rs362305	10114	GUUGGCCCCUCUGCUGUCC	1168	10114	GUUGGCCCCUCUGCUGUCC	1168	10132	GGACAGCAGAGGGGCCAAC	2920
rs362305	10115	UUGGCCCCUCUGCUGUCCU	1169	10115	UUGGCCCCUCUGCUGUCCU	1169	10133	AGGACAGCAGAGGGGCCAA	2921
rs362305	10116	UGGCCCCUCUGCUGUCCUG	1170	10116	UGGCCCCUCUGCUGUCCUG	1170	10134	CAGGACAGCAGAGGGGCCA	2922
rs362305	10117	GGCCCCUCUGCUGUCCUGC	1171	10117	GGCCCCUCUGCUGUCCUGC	1171	10135	GCAGGACAGCAGAGGGGCC	2923
rs362305	10118	GCCCCUCUGCUGUCCUGCA	1172	10118	GCCCCUCUGCUGUCCUGCA	1172	10136	UGCAGGACAGCAGAGGGGC	2924
rs362305	10119	CCCCUCUGCUGUCCUGCAG	1173	10119	CCCCUCUGCUGUCCUGCAG	1173	10137	CUGCAGGACAGCAGAGGGG	2925
rs362305	10120	CCCUCUGCUGUCCUGCAGU	1174	10120	CCCUCUGCUGUCCUGCAGU	1174	10138	ACUGCAGGACAGCAGAGGG	2926
rs362305	10121	CCUCUGCUGUCCUGCAGUA	1175	10121	CCUCUGCUGUCCUGCAGUA	1175	10139	UACUGCAGGACAGCAGAGG	2927
rs362305	10122	CUCUGCUGUCCUGCAGUAG	1176	10122	CUCUGCUGUCCUGCAGUAG	1176	10140	CUACUGCAGGACAGCAGAG	2928
rs362305	10123	UCUGCUGUCCUGCAGUAGA	1177	10123	UCUGCUGUCCUGCAGUAGA	1177	10141	UCUACUGCAGGACAGCAGA	2929
rs362305	10124	CUGCUGUCCUGCAGUAGAA	1178	10124	CUGCUGUCCUGCAGUAGAA	1178	10142	UUCUACUGCAGGACAGCAG	2930
rs362305	10106	GGCUGGCUGUUGGCCCCUG	1179	10106	GGCUGGCUGUUGGCCCCUG	1179	10124	CAGGGGCCAACAGCCAGCC	2931
rs362305	10107	GCUGGCUGUUGGCCCCUGU	1180	10107	GCUGGCUGUUGGCCCCUGU	1180	10125	ACAGGGGCCAACAGCCAGC	2932
rs362305	10108	CUGGCUGUUGGCCCCUGUG	1181	10108	CUGGCUGUUGGCCCCUGUG	1181	10126	CACAGGGGCCAACAGCCAG	2933
rs362305	10109	UGGCUGUUGGCCCCUGUGC	1182	10109	UGGCUGUUGGCCCCUGUGC	1182	10127	GCACAGGGGCCAACAGCCA	2934
rs362305	10110	GGCUGUUGGCCCCUGUGCU	1183	10110	GGCUGUUGGCCCCUGUGCU	1183	10128	AGCACAGGGGCCAACAGCC	2935
rs362305	10111	GCUGUUGGCCCCUGUGCUG	1184	10111	GCUGUUGGCCCCUGUGCUG	1184	10129	CAGCACAGGGGCCAACAGC	2936
rs362305	10112	CUGUUGGCCCCUGUGCUGU	1185	10112	CUGUUGGCCCCUGUGCUGU	1185	10130	ACAGCACAGGGGCCAACAG	2937
rs362305	10113	UGUUGGCCCCUGUGCUGUC	1186	10113	UGUUGGCCCCUGUGCUGUC	1186	10131	GACAGCACAGGGGCCAACA	2938
rs362305	10114	GUUGGCCCCUGUGCUGUCC	1187	10114	GUUGGCCCCUGUGCUGUCC	1187	10132	GGACAGCACAGGGGCCAAC	2939
rs362305	10115	UUGGCCCCUGUGCUGUCCU	1188	10115	UUGGCCCCUGUGCUGUCCU	1188	10133	AGGACAGCACAGGGGCCAA	2940
rs362305	10116	UGGCCCCUGUGCUGUCCUG	1189	10116	UGGCCCCUGUGCUGUCCUG	1189	10134	CAGGACAGCACAGGGGCCA	2941
rs362305	10117	GGCCCCUGUGCUGUCCUGC	1190	10117	GGCCCCUGUGCUGUCCUGC	1190	10135	GCAGGACAGCACAGGGGCC	2942
rs362305	10118	GCCCCUGUGCUGUCCUGCA	1191	10118	GCCCCUGUGCUGUCCUGCA	1191	10136	UGCAGGACAGCACAGGGGC	2943
rs362305	10119	CCCCUGUGCUGUCCUGCAG	1192	10119	CCCCUGUGCUGUCCUGCAG	1192	10137	CUGCAGGACAGCACAGGGG	2944
rs362305	10120	CCCUGUGCUGUCCUGCAGU	1193	10120	CCCUGUGCUGUCCUGCAGU	1193	10138	ACUGCAGGACAGCACAGGG	2945
rs362305	10121	CCUGUGCUGUCCUGCAGUA	1194	10121	CCUGUGCUGUCCUGCAGUA	1194	10139	UACUGCAGGACAGCACAGG	2946
rs362305	10122	CUGUGCUGUCCUGCAGUAG	1195	10122	CUGUGCUGUCCUGCAGUAG	1195	10140	CUACUGCAGGACAGCACAG	2947
rs362305	10123	UGUGCUGUCCUGCAGUAGA	1196	10123	UGUGCUGUCCUGCAGUAGA	1196	10141	UCUACUGCAGGACAGCACA	2948
rs362305	10124	GUGCUGUCCUGCAGUAGAA	1197	10124	GUGCUGUCCUGCAGUAGAA	1197	10142	UUCUACUGCAGGACAGCAC	2949
rs362304	10218	AUGCACAGAUGCCAUGGCC	1198	10218	AUGCACAGAUGCCAUGGCC	1198	10236	GGCCAUGGCAUCUGUGCAU	2950
rs362304	10219	UGCACAGAUGCCAUGGCCU	1199	10219	UGCACAGAUGCCAUGGCCU	1199	10237	AGGCCAUGGCAUCUGUGCA	2951
rs362304	10220	GCACAGAUGCCAUGGCCUG	1200	10220	GCACAGAUGCCAUGGCCUG	1200	10238	CAGGCCAUGGCAUCUGUGC	2952
rs362304	10221	CACAGAUGCCAUGGCCUGU	1201	10221	CACAGAUGCCAUGGCCUGU	1201	10239	ACAGGCCAUGGCAUCUGUG	2953
rs362304	10222	ACAGAUGCCAUGGCCUGUG	1202	10222	ACAGAUGCCAUGGCCUGUG	1202	10240	CACAGGCCAUGGCAUCUGU	2954
rs362304	10223	CAGAUGCCAUGGCCUGUGC	1203	10223	CAGAUGCCAUGGCCUGUGC	1203	10241	GCACAGGCCAUGGCAUCUG	2955
rs362304	10224	AGAUGCCAUGGCCUGUGCU	1204	10224	AGAUGCCAUGGCCUGUGCU	1204	10242	AGCACAGGCCAUGGCAUCU	2956
rs362304	10225	GAUGCCAUGGCCUGUGCUG	1205	10225	GAUGCCAUGGCCUGUGCUG	1205	10243	CAGCACAGGCCAUGGCAUC	2957

rs362304	10226	AUGCCAUGGCCUGUGCUGG	1206	10226	AUGCCAUGGCCUGUGCUGG	1206	10244	CCAGCACAGGCCAUGGCAU	2958
rs362304	10227	UGCCAUGGCCUGUGCUGGG	1207	10227	UGCCAUGGCCUGUGCUGGG	1207	10245	CCCAGCACAGGCCAUGGCA	2959
rs362304	10228	GCCAUGGCCUGUGCUGGGC	1208	10228	GCCAUGGCCUGUGCUGGGC	1208	10246	GCCCAGCACAGGCCAUGGC	2960
rs362304	10229	CCAUGGCCUGUGCUGGGCC	1209	10229	CCAUGGCCUGUGCUGGGCC	1209	10247	GGCCCAGCACAGGCCAUGG	2961
rs362304	10230	CAUGGCCUGUGCUGGGCCA	1210	10230	CAUGGCCUGUGCUGGGCCA	1210	10248	UGGCCCAGCACAGGCCAUG	2962
rs362304	10231	AUGGCCUGUGCUGGGCCAG	1211	10231	AUGGCCUGUGCUGGGCCAG	1211	10249	CUGGCCCAGCACAGGCCAU	2963
rs362304	10232	UGGCCUGUGCUGGGCCAGU	1212	10232	UGGCCUGUGCUGGGCCAGU	1212	10250	ACUGGCCCAGCACAGGCCA	2964
rs362304	10233	GGCCUGUGCUGGGCCAGUG	1213	10233	GGCCUGUGCUGGGCCAGUG	1213	10251	CACUGGCCCAGCACAGGCC	2965
rs362304	10234	GCCUGUGCUGGGCCAGUGG	1214	10234	GCCUGUGCUGGGCCAGUGG	1214	10252	CCACUGGCCCAGCACAGGC	2966
rs362304	10235	CCUGUGCUGGGCCAGUGGC	1215	10235	CCUGUGCUGGGCCAGUGGC	1215	10253	GCCACUGGCCCAGCACAGG	2967
rs362304	10236	CUGUGCUGGGCCAGUGGCU	1216	10236	CUGUGCUGGGCCAGUGGCU	1216	10254	AGCCACUGGCCCAGCACAG	2968
rs362304	10218	AUGCACAGAUGCCAUGGCA	1217	10218	AUGCACAGAUGCCAUGGCA	1217	10236	UGCCAUGGCAUCUGUGCAU	2969
rs362304	10219	UGCACAGAUGCCAUGGCAU	1218	10219	UGCACAGAUGCCAUGGCAU	1218	10237	AUGCCAUGGCAUCUGUGCA	2970
rs362304	10220	GCACAGAUGCCAUGGCAUG	1219	10220	GCACAGAUGCCAUGGCAUG	1219	10238	CAUGCCAUGGCAUCUGUGC	2971
rs362304	10221	CACAGAUGCCAUGGCAUGU	1220	10221	CACAGAUGCCAUGGCAUGU	1220	10239	ACAUGCCAUGGCAUCUGUG	2972
rs362304	10222	ACAGAUGCCAUGGCAUGUG	1221	10222	ACAGAUGCCAUGGCAUGUG	1221	10240	CACAUGCCAUGGCAUCUGU	2973
rs362304	10223	CAGAUGCCAUGGCAUGUGC	1222	10223	CAGAUGCCAUGGCAUGUGC	1222	10241	GCACAUGCCAUGGCAUCUG	2974
rs362304	10224	AGAUGCCAUGGCAUGUGCU	1223	10224	AGAUGCCAUGGCAUGUGCU	1223	10242	AGCACAUGCCAUGGCAUCU	2975
rs362304	10225	GAUGCCAUGGCAUGUGCUG	1224	10225	GAUGCCAUGGCAUGUGCUG	1224	10243	CAGCACAUGCCAUGGCAUC	2976
rs362304	10226	AUGCCAUGGCAUGUGCUGG	1225	10226	AUGCCAUGGCAUGUGCUGG	1225	10244	CCAGCACAUGCCAUGGCAU	2977
rs362304	10227	UGCCAUGGCAUGUGCUGGG	1226	10227	UGCCAUGGCAUGUGCUGGG	1226	10245	CCCAGCACAUGCCAUGGCA	2978
rs362304	10228	GCCAUGGCAUGUGCUGGGC	1227	10228	GCCAUGGCAUGUGCUGGGC	1227	10246	GCCCAGCACAUGCCAUGGC	2979
rs362304	10229	CCAUGGCAUGUGCUGGGCC	1228	10229	CCAUGGCAUGUGCUGGGCC	1228	10247	GGCCCAGCACAUGCCAUGG	2980
rs362304	10230	CAUGGCAUGUGCUGGGCCA	1229	10230	CAUGGCAUGUGCUGGGCCA	1229	10248	UGGCCCAGCACAUGCCAUG	2981
rs362304	10231	AUGGCAUGUGCUGGGCCAG	1230	10231	AUGGCAUGUGCUGGGCCAG	1230	10249	CUGGCCCAGCACAUGCCAU	2982
rs362304	10232	UGGCAUGUGCUGGGCCAGU	1231	10232	UGGCAUGUGCUGGGCCAGU	1231	10250	ACUGGCCCAGCACAUGCCA	2983
rs362304	10233	GGCAUGUGCUGGGCCAGUG	1232	10233	GGCAUGUGCUGGGCCAGUG	1232	10251	CACUGGCCCAGCACAUGCC	2984
rs362304	10234	GCAUGUGCUGGGCCAGUGG	1233	10234	GCAUGUGCUGGGCCAGUGG	1233	10252	CCACUGGCCCAGCACAUGC	2985
rs362304	10235	CAUGUGCUGGGCCAGUGGC	1234	10235	CAUGUGCUGGGCCAGUGGC	1234	10253	GCCACUGGCCCAGCACAUG	2986
rs362304	10236	AUGUGCUGGGCCAGUGGCU	1235	10236	AUGUGCUGGGCCAGUGGCU	1235	10254	AGCCACUGGCCCAGCACAU	2987
rs362303	10253	CUGGGGGUGCUAGACACCC	1236	10253	CUGGGGGUGCUAGACACCC	1236	10271	GGGUGUCUAGCACCCCCAG	2988
rs362303	10254	UGGGGGUGCUAGACACCCG	1237	10254	UGGGGGUGCUAGACACCCG	1237	10272	CGGGUGUCUAGCACCCCCA	2989
rs362303	10255	GGGGGUGCUAGACACCCGG	1238	10255	GGGGGUGCUAGACACCCGG	1238	10273	CCGGGUGUCUAGCACCCCC	2990
rs362303	10256	GGGGUGCUAGACACCCGGC	1239	10256	GGGGUGCUAGACACCCGGC	1239	10274	GCCGGGUGUCUAGCACCCC	2991
rs362303	10257	GGGUGCUAGACACCCGGCA	1240	10257	GGGUGCUAGACACCCGGCA	1240	10275	UGCCGGGUGUCUAGCACCC	2992
rs362303	10258	GGUGCUAGACACCCGGCAC	1241	10258	GGUGCUAGACACCCGGCAC	1241	10276	GUGCCGGGUGUCUAGCACC	2993
rs362303	10259	GUGCUAGACACCCGGCACC	1242	10259	GUGCUAGACACCCGGCACC	1242	10277	GGUGCCGGGUGUCUAGCAC	2994
rs362303	10260	UGCUAGACACCCGGCACCA	1243	10260	UGCUAGACACCCGGCACCA	1243	10278	UGGUGCCGGGUGUCUAGCA	2995
rs362303	10261	GCUAGACACCCGGCACCAU	1244	10261	GCUAGACACCCGGCACCAU	1244	10279	AUGGUGCCGGGUGUCUAGC	2996

rs362303	10262	CUAGACACCCGGCACCAUU	1245	10262	CUAGACACCCGGCACCAUU	1245	10280	AAUGGUGCCGGGUGUCUAG	2997
rs362303	10263	UAGACACCCGGCACCAUUC	1246	10263	UAGACACCCGGCACCAUUC	1246	10281	GAAUGGUGCCGGGUGUCUA	2998
rs362303	10264	AGACACCCGGCACCAUUCU	1247	10264	AGACACCCGGCACCAUUCU	1247	10282	AGAAUGGUGCCGGGUGUCU	2999
rs362303	10265	GACACCCGGCACCAUUCUC	1248	10265	GACACCCGGCACCAUUCUC	1248	10283	GAGAAUGGUGCCGGGUGUC	3000
rs362303	10266	ACACCCGGCACCAUUCUCC	1249	10266	ACACCCGGCACCAUUCUCC	1249	10284	GGAGAAUGGUGCCGGGUGU	3001
rs362303	10267	CACCCGGCACCAUUCUCCC	1250	10267	CACCCGGCACCAUUCUCCC	1250	10285	GGGAGAAUGGUGCCGGGUG	3002
rs362303	10268	ACCCGGCACCAUUCUCCCU	1251	10268	ACCCGGCACCAUUCUCCCU	1251	10286	AGGGAGAAUGGUGCCGGGU	3003
rs362303	10269	CCCGGCACCAUUCUCCCUU	1252	10269	CCCGGCACCAUUCUCCCUU	1252	10287	AAGGGAGAAUGGUGCCGGG	3004
rs362303	10270	CCGGCACCAUUCUCCCUUC	1253	10270	CCGGCACCAUUCUCCCUUC	1253	10288	GAAGGGAGAAUGGUGCCGG	3005
rs362303	10271	CGGCACCAUUCUCCCUUCU	1254	10271	CGGCACCAUUCUCCCUUCU	1254	10289	AGAAGGGAGAAUGGUGCCG	3006
rs362303	10253	CUGGGGGUGCUAGACACCU	1255	10253	CUGGGGGUGCUAGACACCU	1255	10271	AGGUGUCUAGCACCCCCAG	3007
rs362303	10254	UGGGGGUGCUAGACACCUG	1256	10254	UGGGGGUGCUAGACACCUG	1256	10272	CAGGUGUCUAGCACCCCCA	3008
rs362303	10255	GGGGGUGCUAGACACCUGG	1257	10255	GGGGGUGCUAGACACCUGG	1257	10273	CCAGGUGUCUAGCACCCCC	3009
rs362303	10256	GGGGUGCUAGACACCUGGC	1258	10256	GGGGUGCUAGACACCUGGC	1258	10274	GCCAGGUGUCUAGCACCCC	3010
rs362303	10257	GGGUGCUAGACACCUGGCA	1259	10257	GGGUGCUAGACACCUGGCA	1259	10275	UGCCAGGUGUCUAGCACCC	3011
rs362303	10258	GGUGCUAGACACCUGGCAC	1260	10258	GGUGCUAGACACCUGGCAC	1260	10276	GUGCCAGGUGUCUAGCACC	3012
rs362303	10259	GUGCUAGACACCUGGCACC	1261	10259	GUGCUAGACACCUGGCACC	1261	10277	GGUGCCAGGUGUCUAGCAC	3013
rs362303	10260	UGCUAGACACCUGGCACCA	1262	10260	UGCUAGACACCUGGCACCA	1262	10278	UGGUGCCAGGUGUCUAGCA	3014
rs362303	10261	GCUAGACACCUGGCACCAU	1263	10261	GCUAGACACCUGGCACCAU	1263	10279	AUGGUGCCAGGUGUCUAGC	3015
rs362303	10262	CUAGACACCUGGCACCAUU	1264	10262	CUAGACACCUGGCACCAUU	1264	10280	AAUGGUGCCAGGUGUCUAG	3016
rs362303	10263	UAGACACCUGGCACCAUUC	1265	10263	UAGACACCUGGCACCAUUC	1265	10281	GAAUGGUGCCAGGUGUCUA	3017
rs362303	10264	AGACACCUGGCACCAUUCU	1266	10264	AGACACCUGGCACCAUUCU	1266	10282	AGAAUGGUGCCAGGUGUCU	3018
rs362303	10265	GACACCUGGCACCAUUCUC	1267	10265	GACACCUGGCACCAUUCUC	1267	10283	GAGAAUGGUGCCAGGUGUC	3019
rs362303	10266	ACACCUGGCACCAUUCUCC	1268	10266	ACACCUGGCACCAUUCUCC	1268	10284	GGAGAAUGGUGCCAGGUGU	3020
rs362303	10267	CACCUGGCACCAUUCUCCC	1269	10267	CACCUGGCACCAUUCUCCC	1269	10285	GGGAGAAUGGUGCCAGGUG	3021
rs362303	10268	ACCUGGCACCAUUCUCCCU	1270	10268	ACCUGGCACCAUUCUCCCU	1270	10286	AGGGAGAAUGGUGCCAGGU	3022
rs362303	10269	CCUGGCACCAUUCUCCCUU	1271	10269	CCUGGCACCAUUCUCCCUU	1271	10287	AAGGGAGAAUGGUGCCAGG	3023
rs362303	10270	CUGGCACCAUUCUCCCUUC	1272	10270	CUGGCACCAUUCUCCCUUC	1272	10288	GAAGGGAGAAUGGUGCCAG	3024
rs362303	10271	UGGCACCAUUCUCCCUUCU	1273	10271	UGGCACCAUUCUCCCUUCU	1273	10289	AGAAGGGAGAAUGGUGCCA	3025
rs1557210	10861	UGUGUUUUGUCUGAGCCUC	1274	10861	UGUGUUUUGUCUGAGCCUC	1274	10879	GAGGCUCAGACAAAACACA	3026
rs1557210	10862	GUGUUUUGUCUGAGCCUCU	1275	10862	GUGUUUUGUCUGAGCCUCU	1275	10880	AGAGGCUCAGACAAAACAC	3027
rs1557210	10863	UGUUUUGUCUGAGCCUCUC	1276	10863	UGUUUUGUCUGAGCCUCUC	1276	10881	GAGAGGCUCAGACAAAACA	3028
rs1557210	10864	GUUUUGUCUGAGCCUCUCU	1277	10864	GUUUUGUCUGAGCCUCUCU	1277	10882	AGAGAGGCUCAGACAAAAC	3029
rs1557210	10865	UUUUGUCUGAGCCUCUCUC	1278	10865	UUUUGUCUGAGCCUCUCUC	1278	10883	GAGAGAGGCUCAGACAAAA	3030
rs1557210	10866	UUUGUCUGAGCCUCUCUCG	1279	10866	UUUGUCUGAGCCUCUCUCG	1279	10884	CGAGAGAGGCUCAGACAAA	3031
rs1557210	10867	UUGUCUGAGCCUCUCUCGG	1280	10867	UUGUCUGAGCCUCUCUCGG	1280	10885	CCGAGAGAGGCUCAGACAA	3032
rs1557210	10868	UGUCUGAGCCUCUCUCGGU	1281	10868	UGUCUGAGCCUCUCUCGGU	1281	10886	ACCGAGAGAGGCUCAGACA	3033
rs1557210	10869	GUCUGAGCCUCUCUCGGUC	1282	10869	GUCUGAGCCUCUCUCGGUC	1282	10887	GACCGAGAGAGGCUCAGAC	3034
rs1557210	10870	UCUGAGCCUCUCUCGGUCA	1283	10870	UCUGAGCCUCUCUCGGUCA	1283	10888	UGACCGAGAGAGGCUCAGA	3035

rs1557210	10871	CUGAGCCUCUCUCGGUCAA	1284	10871	CUGAGCCUCUCUCGGUCAA	1284	10889	UUGACCGAGAGAGGCUCAG	3036
rs1557210	10872	UGAGCCUCUCUCGGUCAAC	1285	10872	UGAGCCUCUCUCGGUCAAC	1285	10890	GUUGACCGAGAGAGGCUCA	3037
rs1557210	10873	GAGCCUCUCUCGGUCAACA	1286	10873	GAGCCUCUCUCGGUCAACA	1286	10891	UGUUGACCGAGAGAGGCUC	3038
rs1557210	10874	AGCCUCUCUCGGUCAACAG	1287	10874	AGCCUCUCUCGGUCAACAG	1287	10892	CUGUUGACCGAGAGAGGCU	3039
rs1557210	10875	GCCUCUCUCGGUCAACAGC	1288	10875	GCCUCUCUCGGUCAACAGC	1288	10893	GCUGUUGACCGAGAGAGGC	3040
rs1557210	10876	CCUCUCUCGGUCAACAGCA	1289	10876	CCUCUCUCGGUCAACAGCA	1289	10894	UGCUGUUGACCGAGAGAGG	3041
rs1557210	10877	CUCUCUCGGUCAACAGCAA	1290	10877	CUCUCUCGGUCAACAGCAA	1290	10895	UUGCUGUUGACCGAGAGAG	3042
rs1557210	10878	UCUCUCGGUCAACAGCAAA	1291	10878	UCUCUCGGUCAACAGCAAA	1291	10896	UUUGCUGUUGACCGAGAGA	3043
rs1557210	10879	CUCUCGGUCAACAGCAAAG	1292	10879	CUCUCGGUCAACAGCAAAG	1292	10897	CUUUGCUGUUGACCGAGAG	3044
rs1557210	10861	UGUGUUUUGUCUGAGCCUU	1293	10861	UGUGUUUUGUCUGAGCCUU	1293	10879	AAGGCUCAGACAAAACACA	3045
rs1557210	10862	GUGUUUUGUCUGAGCCUUU	1294	10862	GUGUUUUGUCUGAGCCUUU	1294	10880	AAAGGCUCAGACAAAACAC	3046
rs1557210	10863	UGUUUUGUCUGAGCCUUUC	1295	10863	UGUUUUGUCUGAGCCUUUC	1295	10881	GAAAGGCUCAGACAAAACA	3047
rs1557210	10864	GUUUUGUCUGAGCCUUUCU	1296	10864	GUUUUGUCUGAGCCUUUCU	1296	10882	AGAAAGGCUCAGACAAAAC	3048
rs362302	10880	UCUCGGUCAACAGCAAAGC	1297	10880	UCUCGGUCAACAGCAAAGC	1297	10898	GCUUUGCUGUUGACCGAGA	3049
rs362302	10881	CUCGGUCAACAGCAAAGCU	1298	10881	CUCGGUCAACAGCAAAGCU	1298	10899	AGCUUUGCUGUUGACCGAG	3050
rs362302	10882	UCGGUCAACAGCAAAGCUU	1299	10882	UCGGUCAACAGCAAAGCUU	1299	10900	AAGCUUUGCUGUUGACCGA	3051
rs362302	10883	CGGUCAACAGCAAAGCUUG	1300	10883	CGGUCAACAGCAAAGCUUG	1300	10901	CAAGCUUUGCUGUUGACCG	3052
rs362302	10865	UUUUGUCUGAGCCUCUCUU	1301	10865	UUUUGUCUGAGCCUCUCUU	1301	10883	AAGAGAGGCUCAGACAAAA	3053
rs362302	10866	UUUGUCUGAGCCUCUCUUG	1302	10866	UUUGUCUGAGCCUCUCUUG	1302	10884	CAAGAGAGGCUCAGACAAA	3054
rs362302	10867	UUGUCUGAGCCUCUCUUGG	1303	10867	UUGUCUGAGCCUCUCUUGG	1303	10885	CCAAGAGAGGCUCAGACAA	3055
rs362302	10868	UGUCUGAGCCUCUCUUGGU	1304	10868	UGUCUGAGCCUCUCUUGGU	1304	10886	ACCAAGAGAGGCUCAGACA	3056
rs362302	10869	GUCUGAGCCUCUCUUGGUC	1305	10869	GUCUGAGCCUCUCUUGGUC	1305	10887	GACCAAGAGAGGCUCAGAC	3057
rs362302	10870	UCUGAGCCUCUCUUGGUCA	1306	10870	UCUGAGCCUCUCUUGGUCA	1306	10888	UGACCAAGAGAGGCUCAGA	3058
rs362302	10871	CUGAGCCUCUCUUGGUCAA	1307	10871	CUGAGCCUCUCUUGGUCAA	1307	10889	UUGACCAAGAGAGGCUCAG	3059
rs362302	10872	UGAGCCUCUCUUGGUCAAC	1308	10872	UGAGCCUCUCUUGGUCAAC	1308	10890	GUUGACCAAGAGAGGCUCA	3060
rs362302	10873	GAGCCUCUCUUGGUCAACA	1309	10873	GAGCCUCUCUUGGUCAACA	1309	10891	UGUUGACCAAGAGAGGCUC	3061
rs362302	10874	AGCCUCUCUUGGUCAACAG	1310	10874	AGCCUCUCUUGGUCAACAG	1310	10892	CUGUUGACCAAGAGAGGCU	3062
rs362302	10875	GCCUCUCUUGGUCAACAGC	1311	10875	GCCUCUCUUGGUCAACAGC	1311	10893	GCUGUUGACCAAGAGAGGC	3063
rs362302	10876	CCUCUCUUGGUCAACAGCA	1312	10876	CCUCUCUUGGUCAACAGCA	1312	10894	UGCUGUUGACCAAGAGAGG	3064
rs362302	10877	CUCUCUUGGUCAACAGCAA	1313	10877	CUCUCUUGGUCAACAGCAA	1313	10895	UUGCUGUUGACCAAGAGAG	3065
rs362302	10878	UCUCUUGGUCAACAGCAAA	1314	10878	UCUCUUGGUCAACAGCAAA	1314	10896	UUUGCUGUUGACCAAGAGA	3066
rs362302	10879	CUCUUGGUCAACAGCAAAG	1315	10879	CUCUUGGUCAACAGCAAAG	1315	10897	CUUUGCUGUUGACCAAGAG	3067
rs362302	10880	UCUUGGUCAACAGCAAAGC	1316	10880	UCUUGGUCAACAGCAAAGC	1316	10898	GCUUUGCUGUUGACCAAGA	3068
rs362302	10881	CUUGGUCAACAGCAAAGCU	1317	10881	CUUGGUCAACAGCAAAGCU	1317	10899	AGCUUUGCUGUUGACCAAG	3069
rs362302	10882	UUGGUCAACAGCAAAGCUU	1318	10882	UUGGUCAACAGCAAAGCUU	1318	10900	AAGCUUUGCUGUUGACCAA	3070
rs362302	10883	UGGUCAACAGCAAAGCUUG	1319	10883	UGGUCAACAGCAAAGCUUG	1319	10901	CAAGCUUUGCUGUUGACCA	3071
rs3025805	10953	CAGCUGACAUCUUGCACGG	1320	10953	CAGCUGACAUCUUGCACGG	1320	10971	CCGUGCAAGAUGUCAGCUG	3072
rs3025805	10954	AGCUGACAUCUUGCACGGU	1321	10954	AGCUGACAUCUUGCACGGU	1321	10972	ACCGUGCAAGAUGUCAGCU	3073
rs3025805	10955	GCUGACAUCUUGCACGGUG	1322	10955	GCUGACAUCUUGCACGGUG	1322	10973	CACCGUGCAAGAUGUCAGC	3074

rs3025805	10956	CUGACAUCUUGCACGGUGA	1323	10956	CUGACAUCUUGCACGGUGA	1323	10974	UCACCGUGCAAGAUGUCAG	3075
rs3025805	10957	UGACAUCUUGCACGGUGAC	1324	10957	UGACAUCUUGCACGGUGAC	1324	10975	GUCACCGUGCAAGAUGUCA	3076
rs3025805	10958	GACAUCUUGCACGGUGACC	1325	10958	GACAUCUUGCACGGUGACC	1325	10976	GGUCACCGUGCAAGAUGUC	3077
rs3025805	10959	ACAUCUUGCACGGUGACCC	1326	10959	ACAUCUUGCACGGUGACCC	1326	10977	GGGUCACCGUGCAAGAUGU	3078
rs3025805	10960	CAUCUUGCACGGUGACCCC	1327	10960	CAUCUUGCACGGUGACCCC	1327	10978	GGGGUCACCGUGCAAGAUG	3079
rs3025805	10961	AUCUUGCACGGUGACCCCU	1328	10961	AUCUUGCACGGUGACCCCU	1328	10979	AGGGGUCACCGUGCAAGAU	3080
rs3025805	10962	UCUUGCACGGUGACCCCUU	1329	10962	UCUUGCACGGUGACCCCUU	1329	10980	AAGGGGUCACCGUGCAAGA	3081
rs3025805	10963	CUUGCACGGUGACCCCUUU	1330	10963	CUUGCACGGUGACCCCUUU	1330	10981	AAAGGGGUCACCGUGCAAG	3082
rs3025805	10964	UUGCACGGUGACCCCUUUU	1331	10964	UUGCACGGUGACCCCUUUU	1331	10982	AAAAGGGGUCACCGUGCAA	3083
rs3025805	10965	UGCACGGUGACCCCUUUUA	1332	10965	UGCACGGUGACCCCUUUUA	1332	10983	UAAAAGGGGUCACCGUGCA	3084
rs3025805	10966	GCACGGUGACCCCUUUUAG	1333	10966	GCACGGUGACCCCUUUUAG	1333	10984	CUAAAAGGGGUCACCGUGC	3085
rs3025805	10967	CACGGUGACCCCUUUUAGU	1334	10967	CACGGUGACCCCUUUUAGU	1334	10985	ACUAAAAGGGGUCACCGUG	3086
rs3025805	10968	ACGGUGACCCCUUUUAGUC	1335	10968	ACGGUGACCCCUUUUAGUC	1335	10986	GACUAAAAGGGGUCACCGU	3087
rs3025805	10969	CGGUGACCCCUUUUAGUCA	1336	10969	CGGUGACCCCUUUUAGUCA	1336	10987	UGACUAAAAGGGGUCACCG	3088
rs3025805	10970	GGUGACCCCUUUUAGUCAG	1337	10970	GGUGACCCCUUUUAGUCAG	1337	10988	CUGACUAAAAGGGGUCACC	3089
rs3025805	10971	GUGACCCCUUUUAGUCAGG	1338	10971	GUGACCCCUUUUAGUCAGG	1338	10989	CCUGACUAAAAGGGGUCAC	3090
rs3025805	10953	CAGCUGACAUCUUGCACGU	1339	10953	CAGCUGACAUCUUGCACGU	1339	10971	ACGUGCAAGAUGUCAGCUG	3091
rs3025805	10954	AGCUGACAUCUUGCACGUU	1340	10954	AGCUGACAUCUUGCACGUU	1340	10972	AACGUGCAAGAUGUCAGCU	3092
rs3025805	10955	GCUGACAUCUUGCACGUUG	1341	10955	GCUGACAUCUUGCACGUUG	1341	10973	CAACGUGCAAGAUGUCAGC	3093
rs3025805	10956	CUGACAUCUUGCACGUUGA	1342	10956	CUGACAUCUUGCACGUUGA	1342	10974	UCAACGUGCAAGAUGUCAG	3094
rs3025805	10957	UGACAUCUUGCACGUUGAC	1343	10957	UGACAUCUUGCACGUUGAC	1343	10975	GUCAACGUGCAAGAUGUCA	3095
rs3025805	10958	GACAUCUUGCACGUUGACC	1344	10958	GACAUCUUGCACGUUGACC	1344	10976	GGUCAACGUGCAAGAUGUC	3096
rs3025805	10959	ACAUCUUGCACGUUGACCC	1345	10959	ACAUCUUGCACGUUGACCC	1345	10977	GGGUCAACGUGCAAGAUGU	3097
rs3025805	10960	CAUCUUGCACGUUGACCCC	1346	10960	CAUCUUGCACGUUGACCCC	1346	10978	GGGGUCAACGUGCAAGAUG	3098
rs3025805	10961	AUCUUGCACGUUGACCCCU	1347	10961	AUCUUGCACGUUGACCCCU	1347	10979	AGGGGUCAACGUGCAAGAU	3099
rs3025805	10962	UCUUGCACGUUGACCCCUU	1348	10962	UCUUGCACGUUGACCCCUU	1348	10980	AAGGGGUCAACGUGCAAGA	3100
rs3025805	10963	CUUGCACGUUGACCCCUUU	1349	10963	CUUGCACGUUGACCCCUUU	1349	10981	AAAGGGGUCAACGUGCAAG	3101
rs3025805	10964	UUGCACGUUGACCCCUUUU	1350	10964	UUGCACGUUGACCCCUUUU	1350	10982	AAAAGGGGUCAACGUGCAA	3102
rs3025805	10965	UGCACGUUGACCCCUUUUA	1351	10965	UGCACGUUGACCCCUUUUA	1351	10983	UAAAAGGGGUCAACGUGCA	3103
rs3025805	10966	GCACGUUGACCCCUUUUAG	1352	10966	GCACGUUGACCCCUUUUAG	1352	10984	CUAAAAGGGGUCAACGUGC	3104
rs3025805	10967	CACGUUGACCCCUUUUAGU	1353	10967	CACGUUGACCCCUUUUAGU	1353	10985	ACUAAAAGGGGUCAACGUG	3105
rs3025805	10968	ACGUUGACCCCUUUUAGUC	1354	10968	ACGUUGACCCCUUUUAGUC	1354	10986	GACUAAAAGGGGUCAACGU	3106
rs3025805	10969	CGUUGACCCCUUUUAGUCA	1355	10969	CGUUGACCCCUUUUAGUCA	1355	10987	UGACUAAAAGGGGUCAACG	3107
rs3025805	10970	GUUGACCCCUUUUAGUCAG	1356	10970	GUUGACCCCUUUUAGUCAG	1356	10988	CUGACUAAAAGGGGUCAAC	3108
rs3025805	10971	UUGACCCCUUUUAGUCAGG	1357	10971	UUGACCCCUUUUAGUCAGG	1357	10989	CCUGACUAAAAGGGGUCAA	3109
rs362267	11163	UUUGGGAGCUCUGCUUGCC	1358	11163	UUUGGGAGCUCUGCUUGCC	1358	11181	GGCAAGCAGAGCUCCCAAA	3110
rs362267	11164	UUGGGAGCUCUGCUUGCCG	1359	11164	UUGGGAGCUCUGCUUGCCG	1359	11182	CGGCAAGCAGAGCUCCCAA	3111
rs362267	11165	UGGGAGCUCUGCUUGCCGA	1360	11165	UGGGAGCUCUGCUUGCCGA	1360	11183	UCGGCAAGCAGAGCUCCCA	3112
rs362267	11166	GGGAGCUCUGCUUGCCGAC	1361	11166	GGGAGCUCUGCUUGCCGAC	1361	11184	GUCGGCAAGCAGAGCUCCC	3113

rs362267	11167	GGAGCUCUGCUUGCCGACU	1362	11167	GGAGCUCUGCUUGCCGACU	1362	11185	AGUCGGCAAGCAGAGCUCC	3114
rs362267	11168	GAGCUCUGCUUGCCGACUG	1363	11168	GAGCUCUGCUUGCCGACUG	1363	11186	CAGUCGGCAAGCAGAGCUC	3115
rs362267	11169	AGCUCUGCUUGCCGACUGG	1364	11169	AGCUCUGCUUGCCGACUGG	1364	11187	CCAGUCGGCAAGCAGAGCU	3116
rs362267	11170	GCUCUGCUUGCCGACUGGC	1365	11170	GCUCUGCUUGCCGACUGGC	1365	11188	GCCAGUCGGCAAGCAGAGC	3117
rs362267	11171	CUCUGCUUGCCGACUGGCU	1366	11171	CUCUGCUUGCCGACUGGCU	1366	11189	AGCCAGUCGGCAAGCAGAG	3118
rs362267	11172	UCUGCUUGCCGACUGGCUG	1367	11172	UCUGCUUGCCGACUGGCUG	1367	11190	CAGCCAGUCGGCAAGCAGA	3119
rs362267	11173	CUGCUUGCCGACUGGCUGU	1368	11173	CUGCUUGCCGACUGGCUGU	1368	11191	ACAGCCAGUCGGCAAGCAG	3120
rs362267	11174	UGCUUGCCGACUGGCUGUG	1369	11174	UGCUUGCCGACUGGCUGUG	1369	11192	CACAGCCAGUCGGCAAGCA	3121
rs362267	11175	GCUUGCCGACUGGCUGUGA	1370	11175	GCUUGCCGACUGGCUGUGA	1370	11193	UCACAGCCAGUCGGCAAGC	3122
rs362267	11176	CUUGCCGACUGGCUGUGAG	1371	11176	CUUGCCGACUGGCUGUGAG	1371	11194	CUCACAGCCAGUCGGCAAG	3123
rs362267	11177	UUGCCGACUGGCUGUGAGA	1372	11177	UUGCCGACUGGCUGUGAGA	1372	11195	UCUCACAGCCAGUCGGCAA	3124
rs362267	11178	UGCCGACUGGCUGUGAGAC	1373	11178	UGCCGACUGGCUGUGAGAC	1373	11196	GUCUCACAGCCAGUCGGCA	3125
rs362267	11179	GCCGACUGGCUGUGAGACG	1374	11179	GCCGACUGGCUGUGAGACG	1374	11197	CGUCUCACAGCCAGUCGGC	3126
rs362267	11180	CCGACUGGCUGUGAGACGA	1375	11180	CCGACUGGCUGUGAGACGA	1375	11198	UCGUCUCACAGCCAGUCGG	3127
rs362267	11181	CGACUGGCUGUGAGACGAG	1376	11181	CGACUGGCUGUGAGACGAG	1376	11199	CUCGUCUCACAGCCAGUCG	3128
rs362267	11163	UUUGGGAGCUCUGCUUGCU	1377	11163	UUUGGGAGCUCUGCUUGCU	1377	11181	AGCAAGCAGAGCUCCCAAA	3129
rs362267	11164	UUGGGAGCUCUGCUUGCUG	1378	11164	UUGGGAGCUCUGCUUGCUG	1378	11182	CAGCAAGCAGAGCUCCCAA	3130
rs362267	11165	UGGGAGCUCUGCUUGCUGA	1379	11165	UGGGAGCUCUGCUUGCUGA	1379	11183	UCAGCAAGCAGAGCUCCCA	3131
rs362267	11166	GGGAGCUCUGCUUGCUGAC	1380	11166	GGGAGCUCUGCUUGCUGAC	1380	11184	GUCAGCAAGCAGAGCUCCC	3132
rs362267	11167	GGAGCUCUGCUUGCUGACU	1381	11167	GGAGCUCUGCUUGCUGACU	1381	11185	AGUCAGCAAGCAGAGCUCC	3133
rs362267	11168	GAGCUCUGCUUGCUGACUG	1382	11168	GAGCUCUGCUUGCUGACUG	1382	11186	CAGUCAGCAAGCAGAGCUC	3134
rs362267	11169	AGCUCUGCUUGCUGACUGG	1383	11169	AGCUCUGCUUGCUGACUGG	1383	11187	CCAGUCAGCAAGCAGAGCU	3135
rs362267	11170	GCUCUGCUUGCUGACUGGC	1384	11170	GCUCUGCUUGCUGACUGGC	1384	11188	GCCAGUCAGCAAGCAGAGC	3136
rs362267	11171	CUCUGCUUGCUGACUGGCU	1385	11171	CUCUGCUUGCUGACUGGCU	1385	11189	AGCCAGUCAGCAAGCAGAG	3137
rs362267	11172	UCUGCUUGCUGACUGGCUG	1386	11172	UCUGCUUGCUGACUGGCUG	1386	11190	CAGCCAGUCAGCAAGCAGA	3138
rs362267	11173	CUGCUUGCUGACUGGCUGU	1387	11173	CUGCUUGCUGACUGGCUGU	1387	11191	ACAGCCAGUCAGCAAGCAG	3139
rs362267	11174	UGCUUGCUGACUGGCUGUG	1388	11174	UGCUUGCUGACUGGCUGUG	1388	11192	CACAGCCAGUCAGCAAGCA	3140
rs362267	11175	GCUUGCUGACUGGCUGUGA	1389	11175	GCUUGCUGACUGGCUGUGA	1389	11193	UCACAGCCAGUCAGCAAGC	3141
rs362267	11176	CUUGCUGACUGGCUGUGAG	1390	11176	CUUGCUGACUGGCUGUGAG	1390	11194	CUCACAGCCAGUCAGCAAG	3142
rs362267	11177	UUGCUGACUGGCUGUGAGA	1391	11177	UUGCUGACUGGCUGUGAGA	1391	11195	UCUCACAGCCAGUCAGCAA	3143
rs362267	11178	UGCUGACUGGCUGUGAGAC	1392	11178	UGCUGACUGGCUGUGAGAC	1392	11196	GUCUCACAGCCAGUCAGCA	3144
rs362267	11179	GCUGACUGGCUGUGAGACG	1393	11179	GCUGACUGGCUGUGAGACG	1393	11197	CGUCUCACAGCCAGUCAGC	3145
rs362267	11180	CUGACUGGCUGUGAGACGA	1394	11180	CUGACUGGCUGUGAGACGA	1394	11198	UCGUCUCACAGCCAGUCAG	3146
rs362267	11181	UGACUGGCUGUGAGACGAG	1395	11181	UGACUGGCUGUGAGACGAG	1395	11199	CUCGUCUCACAGCCAGUCA	3147
rs362301	11382	UGGCAGCUGGGGAGCAGCU	1396	11382	UGGCAGCUGGGGAGCAGCU	1396	11400	AGCUGCUCCCCAGCUGCCA	3148
rs362301	11383	GGCAGCUGGGGAGCAGCUG	1397	11383	GGCAGCUGGGGAGCAGCUG	1397	11401	CAGCUGCUCCCCAGCUGCC	3149
rs362301	11384	GCAGCUGGGGAGCAGCUGA	1398	11384	GCAGCUGGGGAGCAGCUGA	1398	11402	UCAGCUGCUCCCCAGCUGC	3150
rs362301	11385	CAGCUGGGGAGCAGCUGAG	1399	11385	CAGCUGGGGAGCAGCUGAG	1399	11403	CUCAGCUGCUCCCCAGCUG	3151
rs362301	11386	AGCUGGGGAGCAGCUGAGA	1400	11386	AGCUGGGGAGCAGCUGAGA	1400	11404	UCUCAGCUGCUCCCCAGCU	3152

rs362301	11387	GCUGGGGAGCAGCUGAGAU	1401	11387	GCUGGGGAGCAGCUGAGAU	1401	11405	AUCUCAGCUGCUCCCCAGC	3153
rs362301	11388	CUGGGGAGCAGCUGAGAUG	1402	11388	CUGGGGAGCAGCUGAGAUG	1402	11406	CAUCUCAGCUGCUCCCCAG	3154
rs362301	11389	UGGGGAGCAGCUGAGAUGU	1403	11389	UGGGGAGCAGCUGAGAUGU	1403	11407	ACAUCUCAGCUGCUCCCCA	3155
rs362301	11390	GGGGAGCAGCUGAGAUGUG	1404	11390	GGGGAGCAGCUGAGAUGUG	1404	11408	CACAUCUCAGCUGCUCCCC	3156
rs362301	11391	GGGAGCAGCUGAGAUGUGG	1405	11391	GGGAGCAGCUGAGAUGUGG	1405	11409	CCACAUCUCAGCUGCUCCC	3157
rs362301	11392	GGAGCAGCUGAGAUGUGGA	1406	11392	GGAGCAGCUGAGAUGUGGA	1406	11410	UCCACAUCUCAGCUGCUCC	3158
rs362301	11393	GAGCAGCUGAGAUGUGGAC	1407	11393	GAGCAGCUGAGAUGUGGAC	1407	11411	GUCCACAUCUCAGCUGCUC	3159
rs362301	11394	AGCAGCUGAGAUGUGGACU	1408	11394	AGCAGCUGAGAUGUGGACU	1408	11412	AGUCCACAUCUCAGCUGCU	3160
rs362301	11395	GCAGCUGAGAUGUGGACUU	1409	11395	GCAGCUGAGAUGUGGACUU	1409	11413	AAGUCCACAUCUCAGCUGC	3161
rs362301	11396	CAGCUGAGAUGUGGACUUG	1410	11396	CAGCUGAGAUGUGGACUUG	1410	11414	CAAGUCCACAUCUCAGCUG	3162
rs362301	11397	AGCUGAGAUGUGGACUUGU	1411	11397	AGCUGAGAUGUGGACUUGU	1411	11415	ACAAGUCCACAUCUCAGCU	3163
rs362301	11398	GCUGAGAUGUGGACUUGUA	1412	11398	GCUGAGAUGUGGACUUGUA	1412	11416	UACAAGUCCACAUCUCAGC	3164
rs362301	11399	CUGAGAUGUGGACUUGUAU	1413	11399	CUGAGAUGUGGACUUGUAU	1413	11417	AUACAAGUCCACAUCUCAG	3165
rs362301	11400	UGAGAUGUGGACUUGUAUG	1414	11400	UGAGAUGUGGACUUGUAUG	1414	11418	CAUACAAGUCCACAUCUCA	3166
rs362301	11382	UGGCAGCUGGGGAGCAGCG	1415	11382	UGGCAGCUGGGGAGCAGCG	1415	11400	CGCUGCUCCCCAGCUGCCA	3167
rs362301	11383	GGCAGCUGGGGAGCAGCGG	1416	11383	GGCAGCUGGGGAGCAGCGG	1416	11401	CCGCUGCUCCCCAGCUGCC	3168
rs362301	11384	GCAGCUGGGGAGCAGCGGA	1417	11384	GCAGCUGGGGAGCAGCGGA	1417	11402	UCCGCUGCUCCCCAGCUGC	3169
rs362301	11385	CAGCUGGGGAGCAGCGGAG	1418	11385	CAGCUGGGGAGCAGCGGAG	1418	11403	CUCCGCUGCUCCCCAGCUG	3170
rs362301	11386	AGCUGGGGAGCAGCGGAGA	1419	11386	AGCUGGGGAGCAGCGGAGA	1419	11404	UCUCCGCUGCUCCCCAGCU	3171
rs362301	11387	GCUGGGGAGCAGCGGAGAU	1420	11387	GCUGGGGAGCAGCGGAGAU	1420	11405	AUCUCCGCUGCUCCCCAGC	3172
rs362301	11388	CUGGGGAGCAGCGGAGAUG	1421	11388	CUGGGGAGCAGCGGAGAUG	1421	11406	CAUCUCCGCUGCUCCCCAG	3173
rs362301	11389	UGGGGAGCAGCGGAGAUGU	1422	11389	UGGGGAGCAGCGGAGAUGU	1422	11407	ACAUCUCCGCUGCUCCCCA	3174
rs362301	11390	GGGGAGCAGCGGAGAUGUG	1423	11390	GGGGAGCAGCGGAGAUGUG	1423	11408	CACAUCUCCGCUGCUCCCC	3175
rs362301	11391	GGGAGCAGCGGAGAUGUGG	1424	11391	GGGAGCAGCGGAGAUGUGG	1424	11409	CCACAUCUCCGCUGCUCCC	3176
rs362301	11392	GGAGCAGCGGAGAUGUGGA	1425	11392	GGAGCAGCGGAGAUGUGGA	1425	11410	UCCACAUCUCCGCUGCUCC	3177
rs362301	11393	GAGCAGCGGAGAUGUGGAC	1426	11393	GAGCAGCGGAGAUGUGGAC	1426	11411	GUCCACAUCUCCGCUGCUC	3178
rs362301	11394	AGCAGCGGAGAUGUGGACU	1427	11394	AGCAGCGGAGAUGUGGACU	1427	11412	AGUCCACAUCUCCGCUGCU	3179
rs362301	11395	GCAGCGGAGAUGUGGACUU	1428	11395	GCAGCGGAGAUGUGGACUU	1428	11413	AAGUCCACAUCUCCGCUGC	3180
rs362301	11396	CAGCGGAGAUGUGGACUUG	1429	11396	CAGCGGAGAUGUGGACUUG	1429	11414	CAAGUCCACAUCUCCGCUG	3181
rs362301	11397	AGCGGAGAUGUGGACUUGU	1430	11397	AGCGGAGAUGUGGACUUGU	1430	11415	ACAAGUCCACAUCUCCGCU	3182
rs362301	11398	GCGGAGAUGUGGACUUGUA	1431	11398	GCGGAGAUGUGGACUUGUA	1431	11416	UACAAGUCCACAUCUCCGC	3183
rs362301	11399	CGGAGAUGUGGACUUGUAU	1432	11399	CGGAGAUGUGGACUUGUAU	1432	11417	AUACAAGUCCACAUCUCCG	3184
rs362301	11400	GGAGAUGUGGACUUGUAUG	1433	11400	GGAGAUGUGGACUUGUAUG	1433	11418	CAUACAAGUCCACAUCUCC	3185
rs6148278	11440	AGCUGAAAGGGAGCCCCUG	1434	11440	AGCUGAAAGGGAGCCCCUG	1434	11458	CAGGGGCUCCCUUUCAGCU	3186
rs6148278	11441	GCUGAAAGGGAGCCCCUGC	1435	11441	GCUGAAAGGGAGCCCCUGC	1435	11459	GCAGGGGCUCCCUUUCAGC	3187
rs6148278	11442	CUGAAAGGGAGCCCCUGCU	1436	11442	CUGAAAGGGAGCCCCUGCU	1436	11460	AGCAGGGGCUCCCUUUCAG	3188
rs6148278	11443	UGAAAGGGAGCCCCUGCUC	1437	11443	UGAAAGGGAGCCCCUGCUC	1437	11461	GAGCAGGGGCUCCCUUUCA	3189
rs6148278	11444	GAAAGGGAGCCCCUGCUCA	1438	11444	GAAAGGGAGCCCCUGCUCA	1438	11462	UGAGCAGGGGCUCCCUUUC	3190
rs6148278	11445	AAAGGGAGCCCCUGCUCAA	1439	11445	AAAGGGAGCCCCUGCUCAA	1439	11463	UUGAGCAGGGGCUCCCUUU	3191

rs6148278	11446	AAGGGAGCCCCUGCUCAAA	1440	11446	AAGGGAGCCCCUGCUCAAA	1440	11464	UUUGAGCAGGGGCUCCCUU	3192
rs6148278	11447	AGGGAGCCCCUGCUCAAAG	1441	11447	AGGGAGCCCCUGCUCAAAG	1441	11465	CUUUGAGCAGGGGCUCCCU	3193
rs6148278	11448	GGGAGCCCCUGCUCAAAGG	1442	11448	GGGAGCCCCUGCUCAAAGG	1442	11466	CCUUUGAGCAGGGGCUCCC	3194
rs6148278	11449	GGAGCCCCUGCUCAAAGGG	1443	11449	GGAGCCCCUGCUCAAAGGG	1443	11467	CCCUUUGAGCAGGGGCUCC	3195
rs6148278	11450	GAGCCCCUGCUCAAAGGGA	1444	11450	GAGCCCCUGCUCAAAGGGA	1444	11468	UCCCUUUGAGCAGGGGCUC	3196
rs6148278	11451	AGCCCCUGCUCAAAGGGAG	1445	11451	AGCCCCUGCUCAAAGGGAG	1445	11469	CUCCCUUUGAGCAGGGGCU	3197
rs6148278	11452	GCCCCUGCUCAAAGGGAGC	1446	11452	GCCCCUGCUCAAAGGGAGC	1446	11470	GCUCCCUUUGAGCAGGGGC	3198
rs6148278	11453	CCCCUGCUCAAAGGGAGCC	1447	11453	CCCCUGCUCAAAGGGAGCC	1447	11471	GGCUCCCUUUGAGCAGGGG	3199
rs6148278	11454	CCCUGCUCAAAGGGAGCCC	1448	11454	CCCUGCUCAAAGGGAGCCC	1448	11472	GGGCUCCCUUUGAGCAGGG	3200
rs6148278	11455	CCUGCUCAAAGGGAGCCCC	1449	11455	CCUGCUCAAAGGGAGCCCC	1449	11473	GGGGCUCCCUUUGAGCAGG	3201
rs6148278	11456	CUGCUCAAAGGGAGCCCCU	1450	11456	CUGCUCAAAGGGAGCCCCU	1450	11474	AGGGGCUCCCUUUGAGCAG	3202
rs6148278	11457	UGCUCAAAGGGAGCCCCUC	1451	11457	UGCUCAAAGGGAGCCCCUC	1451	11475	GAGGGGCUCCCUUUGAGCA	3203
rs6148278	11458	GCUCAAAGGGAGCCCCUCC	1452	11458	GCUCAAAGGGAGCCCCUCC	1452	11476	GGAGGGGCUCCCUUUGAGC	3204
rs6148278	11459	CUCAAAGGGAGCCCCUCCU	1453	11459	CUCAAAGGGAGCCCCUCCU	1453	11477	AGGAGGGGCUCCCUUUGAG	3205
rs6148278	11460	UCAAAGGGAGCCCCUCCUC	1454	11460	UCAAAGGGAGCCCCUCCUC	1454	11478	GAGGAGGGGCUCCCUUUGA	3206
rs6148278	11461	CAAAGGGAGCCCCUCCUCU	1455	11461	CAAAGGGAGCCCCUCCUCU	1455	11479	AGAGGAGGGGCUCCCUUUG	3207
rs6148278	11440	AGCUGAAAGGGAGCCCCUC	1456	11440	AGCUGAAAGGGAGCCCCUC	1456	11458	GAGGGGCUCCCUUUCAGCU	3208
rs6148278	11441	GCUGAAAGGGAGCCCCUCC	1457	11441	GCUGAAAGGGAGCCCCUCC	1457	11459	GGAGGGGCUCCCUUUCAGC	3209
rs6148278	11442	CUGAAAGGGAGCCCCUCCU	1458	11442	CUGAAAGGGAGCCCCUCCU	1458	11460	AGGAGGGGCUCCCUUUCAG	3210
rs6148278	11443	UGAAAGGGAGCCCCUCCUC	1459	11443	UGAAAGGGAGCCCCUCCUC	1459	11461	GAGGAGGGGCUCCCUUUCA	3211
rs6148278	11444	GAAAGGGAGCCCCUCCUCU	1460	11444	GAAAGGGAGCCCCUCCUCU	1460	11462	AGAGGAGGGGCUCCCUUUC	3212
rs5855773	11641	GUAAGAAAAUCACCAUUCU	1461	11641	GUAAGAAAAUCACCAUUCU	1461	11659	AGAAUGGUGAUUUUCUUAC	3213
rs5855773	11642	UAAGAAAAUCACCAUUCUU	1462	11642	UAAGAAAAUCACCAUUCUU	1462	11660	AAGAAUGGUGAUUUUCUUA	3214
rs5855773	11643	AAGAAAAUCACCAUUCUUC	1463	11643	AAGAAAAUCACCAUUCUUC	1463	11661	GAAGAAUGGUGAUUUUCUU	3215
rs5855773	11644	AGAAAAUCACCAUUCUUCC	1464	11644	AGAAAAUCACCAUUCUUCC	1464	11662	GGAAGAAUGGUGAUUUUCU	3216
rs5855773	11645	GAAAAUCACCAUUCUUCCG	1465	11645	GAAAAUCACCAUUCUUCCG	1465	11663	CGGAAGAAUGGUGAUUUUC	3217
rs5855773	11646	AAAAUCACCAUUCUUCCGU	1466	11646	AAAAUCACCAUUCUUCCGU	1466	11664	ACGGAAGAAUGGUGAUUUU	3218
rs5855773	11647	AAAUCACCAUUCUUCCGUA	1467	11647	AAAUCACCAUUCUUCCGUA	1467	11665	UACGGAAGAAUGGUGAUUU	3219
rs5855773	11648	AAUCACCAUUCUUCCGUAU	1468	11648	AAUCACCAUUCUUCCGUAU	1468	11666	AUACGGAAGAAUGGUGAUU	3220
rs5855773	11649	AUCACCAUUCUUCCGUAUU	1469	11649	AUCACCAUUCUUCCGUAUU	1469	11667	AAUACGGAAGAAUGGUGAU	3221
rs5855773	11650	UCACCAUUCUUCCGUAUUG	1470	11650	UCACCAUUCUUCCGUAUUG	1470	11668	CAAUACGGAAGAAUGGUGA	3222
rs5855773	11651	CACCAUUCUUCCGUAUUGG	1471	11651	CACCAUUCUUCCGUAUUGG	1471	11669	CCAAUACGGAAGAAUGGUG	3223
rs5855773	11652	ACCAUUCUUCCGUAUUGGU	1472	11652	ACCAUUCUUCCGUAUUGGU	1472	11670	ACCAAUACGGAAGAAUGGU	3224
rs5855773	11653	CCAUUCUUCCGUAUUGGUU	1473	11653	CCAUUCUUCCGUAUUGGUU	1473	11671	AACCAAUACGGAAGAAUGG	3225
rs5855773	11654	CAUUCUUCCGUAUUGGUUG	1474	11654	CAUUCUUCCGUAUUGGUUG	1474	11672	CAACCAAUACGGAAGAAUG	3226
rs5855773	11655	AUUCUUCCGUAUUGGUUGG	1475	11655	AUUCUUCCGUAUUGGUUGG	1475	11673	CCAACCAAUACGGAAGAAU	3227
rs5855773	11656	UUCUUCCGUAUUGGUUGGG	1476	11656	UUCUUCCGUAUUGGUUGGG	1476	11674	CCCAACCAAUACGGAAGAA	3228
rs5855773	11641	GUAAGAAAAUCACCAUUCC	1477	11641	GUAAGAAAAUCACCAUUCC	1477	11659	GGAAUGGUGAUUUUCUUAC	3229
rs5855773	11642	UAAGAAAAUCACCAUUCCG	1478	11642	UAAGAAAAUCACCAUUCCG	1478	11660	CGGAAUGGUGAUUUUCUUA	3230

rs5855773	11643	AAGAAAAUCACCAUUCCGU	1479	11643	AAGAAAAUCACCAUUCCGU	1479	11661	ACGGAAUGGUGAUUUUCUU	3231
rs5855773	11644	AGAAAAUCACCAUUCCGUA	1480	11644	AGAAAAUCACCAUUCCGUA	1480	11662	UACGGAAUGGUGAUUUUCU	3232
rs5855773	11645	GAAAAUCACCAUUCCGUAU	1481	11645	GAAAAUCACCAUUCCGUAU	1481	11663	AUACGGAAUGGUGAUUUUC	3233
rs5855773	11646	AAAAUCACCAUUCCGUAUU	1482	11646	AAAAUCACCAUUCCGUAUU	1482	11664	AAUACGGAAUGGUGAUUUU	3234
rs5855773	11647	AAAUCACCAUUCCGUAUUG	1483	11647	AAAUCACCAUUCCGUAUUG	1483	11665	CAAUACGGAAUGGUGAUUU	3235
rs5855773	11648	AAUCACCAUUCCGUAUUGG	1484	11648	AAUCACCAUUCCGUAUUGG	1484	11666	CCAAUACGGAAUGGUGAUU	3236
rs5855773	11649	AUCACCAUUCCGUAUUGGU	1485	11649	AUCACCAUUCCGUAUUGGU	1485	11667	ACCAAUACGGAAUGGUGAU	3237
rs5855773	11650	UCACCAUUCCGUAUUGGUU	1486	11650	UCACCAUUCCGUAUUGGUU	1486	11668	AACCAAUACGGAAUGGUGA	3238
rs5855773	11651	CACCAUUCCGUAUUGGUUG	1487	11651	CACCAUUCCGUAUUGGUUG	1487	11669	CAACCAAUACGGAAUGGUG	3239
rs5855773	11652	ACCAUUCCGUAUUGGUUGG	1488	11652	ACCAUUCCGUAUUGGUUGG	1488	11670	CCAACCAAUACGGAAUGGU	3240
rs5855773	11653	CCAUUCCGUAUUGGUUGGG	1489	11653	CCAUUCCGUAUUGGUUGGG	1489	11671	CCCAACCAAUACGGAAUGG	3241
rs5855774	11740	AAGUUCUCAGAACUGUUGC	1490	11740	AAGUUCUCAGAACUGUUGC	1490	11758	GCAACAGUUCUGAGAACUU	3242
rs5855774	11741	AGUUCUCAGAACUGUUGCU	1491	11741	AGUUCUCAGAACUGUUGCU	1491	11759	AGCAACAGUUCUGAGAACU	3243
rs5855774	11742	GUUCUCAGAACUGUUGCUG	1492	11742	GUUCUCAGAACUGUUGCUG	1492	11760	CAGCAACAGUUCUGAGAAC	3244
rs5855774	11743	UUCUCAGAACUGUUGCUGC	1493	11743	UUCUCAGAACUGUUGCUGC	1493	11761	GCAGCAACAGUUCUGAGAA	3245
rs5855774	11744	UCUCAGAACUGUUGCUGCU	1494	11744	UCUCAGAACUGUUGCUGCU	1494	11762	AGCAGCAACAGUUCUGAGA	3246
rs5855774	11745	CUCAGAACUGUUGCUGCUC	1495	11745	CUCAGAACUGUUGCUGCUC	1495	11763	GAGCAGCAACAGUUCUGAG	3247
rs5855774	11746	UCAGAACUGUUGCUGCUCC	1496	11746	UCAGAACUGUUGCUGCUCC	1496	11764	GGAGCAGCAACAGUUCUGA	3248
rs5855774	11747	CAGAACUGUUGCUGCUCCC	1497	11747	CAGAACUGUUGCUGCUCCC	1497	11765	GGGAGCAGCAACAGUUCUG	3249
rs5855774	11748	AGAACUGUUGCUGCUCCCC	1498	11748	AGAACUGUUGCUGCUCCCC	1498	11766	GGGGAGCAGCAACAGUUCU	3250
rs5855774	11749	GAACUGUUGCUGCUCCCCA	1499	11749	GAACUGUUGCUGCUCCCCA	1499	11767	UGGGGAGCAGCAACAGUUC	3251
rs5855774	11750	AACUGUUGCUGCUCCCCAC	1500	11750	AACUGUUGCUGCUCCCCAC	1500	11768	GUGGGGAGCAGCAACAGUU	3252
rs5855774	11751	ACUGUUGCUGCUCCCCACC	1501	11751	ACUGUUGCUGCUCCCCACC	1501	11769	GGUGGGGAGCAGCAACAGU	3253
rs5855774	11752	CUGUUGCUGCUCCCCACCC	1502	11752	CUGUUGCUGCUCCCCACCC	1502	11770	GGGUGGGGAGCAGCAACAG	3254
rs5855774	11753	UGUUGCUGCUCCCCACCCG	1503	11753	UGUUGCUGCUCCCCACCCG	1503	11771	CGGGUGGGGAGCAGCAACA	3255
rs5855774	11754	GUUGCUGCUCCCCACCCGC	1504	11754	GUUGCUGCUCCCCACCCGC	1504	11772	GCGGGUGGGGAGCAGCAAC	3256
rs5855774	11755	UUGCUGCUCCCCACCCGCC	1505	11755	UUGCUGCUCCCCACCCGCC	1505	11773	GGCGGGUGGGGAGCAGCAA	3257
rs5855774	11756	UGCUGCUCCCCACCCGCCU	1506	11756	UGCUGCUCCCCACCCGCCU	1506	11774	AGGCGGGUGGGGAGCAGCA	3258
rs5855774	11740	AAGUUCUCAGAACUGUUGG	1507	11740	AAGUUCUCAGAACUGUUGG	1507	11758	CCAACAGUUCUGAGAACUU	3259
rs5855774	11741	AGUUCUCAGAACUGUUGGC	1508	11741	AGUUCUCAGAACUGUUGGC	1508	11759	GCCAACAGUUCUGAGAACU	3260
rs5855774	11742	GUUCUCAGAACUGUUGGCU	1509	11742	GUUCUCAGAACUGUUGGCU	1509	11760	AGCCAACAGUUCUGAGAAC	3261
rs5855774	11743	UUCUCAGAACUGUUGGCUG	1510	11743	UUCUCAGAACUGUUGGCUG	1510	11761	CAGCCAACAGUUCUGAGAA	3262
rs5855774	11744	UCUCAGAACUGUUGGCUGC	1511	11744	UCUCAGAACUGUUGGCUGC	1511	11762	GCAGCCAACAGUUCUGAGA	3263
rs5855774	11745	CUCAGAACUGUUGGCUGCU	1512	11745	CUCAGAACUGUUGGCUGCU	1512	11763	AGCAGCCAACAGUUCUGAG	3264
rs5855774	11746	UCAGAACUGUUGGCUGCUC	1513	11746	UCAGAACUGUUGGCUGCUC	1513	11764	GAGCAGCCAACAGUUCUGA	3265
rs5855774	11747	CAGAACUGUUGGCUGCUCC	1514	11747	CAGAACUGUUGGCUGCUCC	1514	11765	GGAGCAGCCAACAGUUCUG	3266
rs5855774	11748	AGAACUGUUGGCUGCUCCC	1515	11748	AGAACUGUUGGCUGCUCCC	1515	11766	GGGAGCAGCCAACAGUUCU	3267
rs5855774	11749	GAACUGUUGGCUGCUCCCC	1516	11749	GAACUGUUGGCUGCUCCCC	1516	11767	GGGGAGCAGCCAACAGUUC	3268
rs5855774	11750	AACUGUUGGCUGCUCCCCA	1517	11750	AACUGUUGGCUGCUCCCCA	1517	11768	UGGGGAGCAGCCAACAGUU	3269

rs5855774	11751	ACUGUUGGCUGCUCCCCAC	1518	11751	ACUGUUGGCUGCUCCCCAC	1518	11769	GUGGGGAGCAGCCAACAGU	3270
rs5855774	11752	CUGUUGGCUGCUCCCCACC	1519	11752	CUGUUGGCUGCUCCCCACC	1519	11770	GGUGGGGAGCAGCCAACAG	3271
rs5855774	11753	UGUUGGCUGCUCCCCACCC	1520	11753	UGUUGGCUGCUCCCCACCC	1520	11771	GGGUGGGGAGCAGCCAACA	3272
rs5855774	11754	GUUGGCUGCUCCCCACCCG	1521	11754	GUUGGCUGCUCCCCACCCG	1521	11772	CGGGUGGGGAGCAGCCAAC	3273
rs5855774	11755	UUGGCUGCUCCCCACCCGC	1522	11755	UUGGCUGCUCCCCACCCGC	1522	11773	GCGGGUGGGGAGCAGCCAA	3274
rs5855774	11756	UGGCUGCUCCCCACCCGCC	1523	11756	UGGCUGCUCCCCACCCGCC	1523	11774	GGCGGGUGGGGAGCAGCCA	3275
rs5855774	11757	GGCUGCUCCCCACCCGCCU	1524	11757	GGCUGCUCCCCACCCGCCU	1524	11775	AGGCGGGUGGGGAGCAGCC	3276
rs2159172	11846	AGAUGUUUACAUUUGUAAG	1525	11846	AGAUGUUUACAUUUGUAAG	1525	11864	CUUACAAAUGUAAACAUCU	3277
rs2159172	11847	GAUGUUUACAUUUGUAAGA	1526	11847	GAUGUUUACAUUUGUAAGA	1526	11865	UCUUACAAAUGUAAACAUC	3278
rs2159172	11848	AUGUUUACAUUUGUAAGAA	1527	11848	AUGUUUACAUUUGUAAGAA	1527	11866	UUCUUACAAAUGUAAACAU	3279
rs2159172	11849	UGUUUACAUUUGUAAGAAA	1528	11849	UGUUUACAUUUGUAAGAAA	1528	11867	UUUCUUACAAAUGUAAACA	3280
rs2159172	11850	GUUUACAUUUGUAAGAAAU	1529	11850	GUUUACAUUUGUAAGAAAU	1529	11868	AUUUCUUACAAAUGUAAAC	3281
rs2159172	11851	UUUACAUUUGUAAGAAAUA	1530	11851	UUUACAUUUGUAAGAAAUA	1530	11869	UAUUUCUUACAAAUGUAAA	3282
rs2159172	11852	UUACAUUUGUAAGAAAUAA	1531	11852	UUACAUUUGUAAGAAAUAA	1531	11870	UUAUUUCUUACAAAUGUAA	3283
rs2159172	11853	UACAUUUGUAAGAAAUAAC	1532	11853	UACAUUUGUAAGAAAUAAC	1532	11871	GUUAUUUCUUACAAAUGUA	3284
rs2159172	11854	ACAUUUGUAAGAAAUAACA	1533	11854	ACAUUUGUAAGAAAUAACA	1533	11872	UGUUAUUUCUUACAAAUGU	3285
rs2159172	11855	CAUUUGUAAGAAAUAACAC	1534	11855	CAUUUGUAAGAAAUAACAC	1534	11873	GUGUUAUUUCUUACAAAUG	3286
rs2159172	11856	AUUUGUAAGAAAUAACACU	1535	11856	AUUUGUAAGAAAUAACACU	1535	11874	AGUGUUAUUUCUUACAAAU	3287
rs2159172	11857	UUUGUAAGAAAUAACACUG	1536	11857	UUUGUAAGAAAUAACACUG	1536	11875	CAGUGUUAUUUCUUACAAA	3288
rs2159172	11858	UUGUAAGAAAUAACACUGU	1537	11858	UUGUAAGAAAUAACACUGU	1537	11876	ACAGUGUUAUUUCUUACAA	3289
rs2159172	11859	UGUAAGAAAUAACACUGUG	1538	11859	UGUAAGAAAUAACACUGUG	1538	11877	CACAGUGUUAUUUCUUACA	3290
rs2159172	11860	GUAAGAAAUAACACUGUGA	1539	11860	GUAAGAAAUAACACUGUGA	1539	11878	UCACAGUGUUAUUUCUUAC	3291
rs2159172	11861	UAAGAAAUAACACUGUGAA	1540	11861	UAAGAAAUAACACUGUGAA	1540	11879	UUCACAGUGUUAUUUCUUA	3292
rs2159172	11862	AAGAAAUAACACUGUGAAU	1541	11862	AAGAAAUAACACUGUGAAU	1541	11880	AUUCACAGUGUUAUUUCUU	3293
rs2159172	11863	AGAAAUAACACUGUGAAUG	1542	11863	AGAAAUAACACUGUGAAUG	1542	11881	CAUUCACAGUGUUAUUUCU	3294
rs2159172	11864	GAAAUAACACUGUGAAUGU	1543	11864	GAAAUAACACUGUGAAUGU	1543	11882	ACAUUCACAGUGUUAUUUC	3295
rs2159172	11846	AGAUGUUUACAUUUGUAAA	1544	11846	AGAUGUUUACAUUUGUAAA	1544	11864	UUUACAAAUGUAAACAUCU	3296
rs2159172	11847	GAUGUUUACAUUUGUAAAA	1545	11847	GAUGUUUACAUUUGUAAAA	1545	11865	UUUUACAAAUGUAAACAUC	3297
rs2159172	11848	AUGUUUACAUUUGUAAAAA	1546	11848	AUGUUUACAUUUGUAAAAA	1546	11866	UUUUUACAAAUGUAAACAU	3298
rs2159172	11849	UGUUUACAUUUGUAAAAAA	1547	11849	UGUUUACAUUUGUAAAAAA	1547	11867	UUUUUUACAAAUGUAAACA	3299
rs2159172	11850	GUUUACAUUUGUAAAAAAU	1548	11850	GUUUACAUUUGUAAAAAAU	1548	11868	AUUUUUUACAAAUGUAAAC	3300
rs2159172	11851	UUUACAUUUGUAAAAAAUA	1549	11851	UUUACAUUUGUAAAAAAUA	1549	11869	UAUUUUUUACAAAUGUAAA	3301
rs2159172	11852	UUACAUUUGUAAAAAAUAA	1550	11852	UUACAUUUGUAAAAAAUAA	1550	11870	UUAUUUUUUACAAAUGUAA	3302
rs2159172	11853	UACAUUUGUAAAAAAUAAC	1551	11853	UACAUUUGUAAAAAAUAAC	1551	11871	GUUAUUUUUUACAAAUGUA	3303
rs2159172	11854	ACAUUUGUAAAAAAUAACA	1552	11854	ACAUUUGUAAAAAAUAACA	1552	11872	UGUUAUUUUUUACAAAUGU	3304
rs2159172	11855	CAUUUGUAAAAAAUAACAC	1553	11855	CAUUUGUAAAAAAUAACAC	1553	11873	GUGUUAUUUUUUACAAAUG	3305
rs2159172	11856	AUUUGUAAAAAAUAACACU	1554	11856	AUUUGUAAAAAAUAACACU	1554	11874	AGUGUUAUUUUUUACAAAU	3306
rs2159172	11857	UUUGUAAAAAAUAACACUG	1555	11857	UUUGUAAAAAAUAACACUG	1555	11875	CAGUGUUAUUUUUUACAAA	3307
rs2159172	11858	UUGUAAAAAAUAACACUGU	1556	11858	UUGUAAAAAAUAACACUGU	1556	11876	ACAGUGUUAUUUUUUACAA	3308

rs2159172	11859	UGUAAAAAAUAACACUGUG	1557	11859	UGUAAAAAAUAACACUGUG	1557	11877	CACAGUGUUAUUUUUUACA	3309
rs2159172	11860	GUAAAAAAUAACACUGUGA	1558	11860	GUAAAAAAUAACACUGUGA	1558	11878	UCACAGUGUUAUUUUUUAC	3310
rs2159172	11861	UAAAAAAUAACACUGUGAA	1559	11861	UAAAAAAUAACACUGUGAA	1559	11879	UUCACAGUGUUAUUUUUUA	3311
rs2159172	11862	AAAAAAUAACACUGUGAAU	1560	11862	AAAAAAUAACACUGUGAAU	1560	11880	AUUCACAGUGUUAUUUUUU	3312
rs2159172	11863	AAAAAUAACACUGUGAAUG	1561	11863	AAAAAUAACACUGUGAAUG	1561	11881	CAUUCACAGUGUUAUUUUU	3313
rs2159172	11864	AAAAUAACACUGUGAAUGU	1562	11864	AAAAUAACACUGUGAAUGU	1562	11882	ACAUUCACAGUGUUAUUUU	3314
rs2237008	12640	ACCCUCAUUUCUGCCAGCG	1563	12640	ACCCUCAUUUCUGCCAGCG	1563	12658	CGCUGGCAGAAAUGAGGGU	3315
rs2237008	12641	CCCUCAUUUCUGCCAGCGC	1564	12641	CCCUCAUUUCUGCCAGCGC	1564	12659	GCGCUGGCAGAAAUGAGGG	3316
rs2237008	12642	CCUCAUUUCUGCCAGCGCA	1565	12642	CCUCAUUUCUGCCAGCGCA	1565	12660	UGCGCUGGCAGAAAUGAGG	3317
rs2237008	12643	CUCAUUUCUGCCAGCGCAU	1566	12643	CUCAUUUCUGCCAGCGCAU	1566	12661	AUGCGCUGGCAGAAAUGAG	3318
rs2237008	12644	UCAUUUCUGCCAGCGCAUG	1567	12644	UCAUUUCUGCCAGCGCAUG	1567	12662	CAUGCGCUGGCAGAAAUGA	3319
rs2237008	12645	CAUUUCUGCCAGCGCAUGU	1568	12645	CAUUUCUGCCAGCGCAUGU	1568	12663	ACAUGCGCUGGCAGAAAUG	3320
rs2237008	12646	AUUUCUGCCAGCGCAUGUG	1569	12646	AUUUCUGCCAGCGCAUGUG	1569	12664	CACAUGCGCUGGCAGAAAU	3321
rs2237008	12647	UUUCUGCCAGCGCAUGUGU	1570	12647	UUUCUGCCAGCGCAUGUGU	1570	12665	ACACAUGCGCUGGCAGAAA	3322
rs2237008	12648	UUCUGCCAGCGCAUGUGUC	1571	12648	UUCUGCCAGCGCAUGUGUC	1571	12666	GACACAUGCGCUGGCAGAA	3323
rs2237008	12649	UCUGCCAGCGCAUGUGUCC	1572	12649	UCUGCCAGCGCAUGUGUCC	1572	12667	GGACACAUGCGCUGGCAGA	3324
rs2237008	12650	CUGCCAGCGCAUGUGUCCU	1573	12650	CUGCCAGCGCAUGUGUCCU	1573	12668	AGGACACAUGCGCUGGCAG	3325
rs2237008	12651	UGCCAGCGCAUGUGUCCUU	1574	12651	UGCCAGCGCAUGUGUCCUU	1574	12669	AAGGACACAUGCGCUGGCA	3326
rs2237008	12652	GCCAGCGCAUGUGUCCUUU	1575	12652	GCCAGCGCAUGUGUCCUUU	1575	12670	AAAGGACACAUGCGCUGGC	3327
rs2237008	12653	CCAGCGCAUGUGUCCUUUC	1576	12653	CCAGCGCAUGUGUCCUUUC	1576	12671	GAAAGGACACAUGCGCUGG	3328
rs2237008	12654	CAGCGCAUGUGUCCUUUCA	1577	12654	CAGCGCAUGUGUCCUUUCA	1577	12672	UGAAAGGACACAUGCGCUG	3329
rs2237008	12655	AGCGCAUGUGUCCUUUCAA	1578	12655	AGCGCAUGUGUCCUUUCAA	1578	12673	UUGAAAGGACACAUGCGCU	3330
rs2237008	12656	GCGCAUGUGUCCUUUCAAG	1579	12656	GCGCAUGUGUCCUUUCAAG	1579	12674	CUUGAAAGGACACAUGCGC	3331
rs2237008	12657	CGCAUGUGUCCUUUCAAGG	1580	12657	CGCAUGUGUCCUUUCAAGG	1580	12675	CCUUGAAAGGACACAUGCG	3332
rs2237008	12658	GCAUGUGUCCUUUCAAGGG	1581	12658	GCAUGUGUCCUUUCAAGGG	1581	12676	CCCUUGAAAGGACACAUGC	3333
rs2237008	12640	ACCCUCAUUUCUGCCAGCA	1582	12640	ACCCUCAUUUCUGCCAGCA	1582	12658	UGCUGGCAGAAAUGAGGGU	3334
rs2237008	12641	CCCUCAUUUCUGCCAGCAC	1583	12641	CCCUCAUUUCUGCCAGCAC	1583	12659	GUGCUGGCAGAAAUGAGGG	3335
rs2237008	12642	CCUCAUUUCUGCCAGCACA	1584	12642	CCUCAUUUCUGCCAGCACA	1584	12660	UGUGCUGGCAGAAAUGAGG	3336
rs2237008	12643	CUCAUUUCUGCCAGCACAU	1585	12643	CUCAUUUCUGCCAGCACAU	1585	12661	AUGUGCUGGCAGAAAUGAG	3337
rs2237008	12644	UCAUUUCUGCCAGCACAUG	1586	12644	UCAUUUCUGCCAGCACAUG	1586	12662	CAUGUGCUGGCAGAAAUGA	3338
rs2237008	12645	CAUUUCUGCCAGCACAUGU	1587	12645	CAUUUCUGCCAGCACAUGU	1587	12663	ACAUGUGCUGGCAGAAAUG	3339
rs2237008	12646	AUUUCUGCCAGCACAUGUG	1588	12646	AUUUCUGCCAGCACAUGUG	1588	12664	CACAUGUGCUGGCAGAAAU	3340
rs2237008	12647	UUUCUGCCAGCACAUGUGU	1589	12647	UUUCUGCCAGCACAUGUGU	1589	12665	ACACAUGUGCUGGCAGAAA	3341
rs2237008	12648	UUCUGCCAGCACAUGUGUC	1590	12648	UUCUGCCAGCACAUGUGUC	1590	12666	GACACAUGUGCUGGCAGAA	3342
rs2237008	12649	UCUGCCAGCACAUGUGUCC	1591	12649	UCUGCCAGCACAUGUGUCC	1591	12667	GGACACAUGUGCUGGCAGA	3343
rs2237008	12650	CUGCCAGCACAUGUGUCCU	1592	12650	CUGCCAGCACAUGUGUCCU	1592	12668	AGGACACAUGUGCUGGCAG	3344
rs2237008	12651	UGCCAGCACAUGUGUCCUU	1593	12651	UGCCAGCACAUGUGUCCUU	1593	12669	AAGGACACAUGUGCUGGCA	3345
rs2237008	12652	GCCAGCACAUGUGUCCUUU	1594	12652	GCCAGCACAUGUGUCCUUU	1594	12670	AAAGGACACAUGUGCUGGC	3346
rs2237008	12653	CCAGCACAUGUGUCCUUUC	1595	12653	CCAGCACAUGUGUCCUUUC	1595	12671	GAAAGGACACAUGUGCUGG	3347

rs2237008	12654	CAGCACAUGUGUCCUUUCA	1596	12654	CAGCACAUGUGUCCUUUCA	1596	12672	UGAAAGGACACAUGUGCUG	3348
rs2237008	12655	AGCACAUGUGUCCUUUCAA	1597	12655	AGCACAUGUGUCCUUUCAA	1597	12673	UUGAAAGGACACAUGUGCU	3349
rs2237008	12656	GCACAUGUGUCCUUUCAAG	1598	12656	GCACAUGUGUCCUUUCAAG	1598	12674	CUUGAAAGGACACAUGUGC	3350
rs2237008	12657	CACAUGUGUCCUUUCAAGG	1599	12657	CACAUGUGUCCUUUCAAGG	1599	12675	CCUUGAAAGGACACAUGUG	3351
rs2237008	12658	ACAUGUGUCCUUUCAAGGG	1600	12658	ACAUGUGUCCUUUCAAGGG	1600	12676	CCCUUGAAAGGACACAUGU	3352
rs362300	12893	CAGGUGGAACUUCCUCCCG	1601	12893	CAGGUGGAACUUCCUCCCG	1601	12911	CGGGAGGAAGUUCCACCUG	3353
rs362300	12894	AGGUGGAACUUCCUCCCGU	1602	12894	AGGUGGAACUUCCUCCCGU	1602	12912	ACGGGAGGAAGUUCCACCU	3354
rs362300	12895	GGUGGAACUUCCUCCCGUU	1603	12895	GGUGGAACUUCCUCCCGUU	1603	12913	AACGGGAGGAAGUUCCACC	3355
rs362300	12896	GUGGAACUUCCUCCCGUUG	1604	12896	GUGGAACUUCCUCCCGUUG	1604	12914	CAACGGGAGGAAGUUCCAC	3356
rs362300	12897	UGGAACUUCCUCCCGUUGC	1605	12897	UGGAACUUCCUCCCGUUGC	1605	12915	GCAACGGGAGGAAGUUCCA	3357
rs362300	12898	GGAACUUCCUCCCGUUGCG	1606	12898	GGAACUUCCUCCCGUUGCG	1606	12916	CGCAACGGGAGGAAGUUCC	3358
rs362300	12899	GAACUUCCUCCCGUUGCGG	1607	12899	GAACUUCCUCCCGUUGCGG	1607	12917	CCGCAACGGGAGGAAGUUC	3359
rs362300	12900	AACUUCCUCCCGUUGCGGG	1608	12900	AACUUCCUCCCGUUGCGGG	1608	12918	CCCGCAACGGGAGGAAGUU	3360
rs362300	12901	ACUUCCUCCCGUUGCGGGG	1609	12901	ACUUCCUCCCGUUGCGGGG	1609	12919	CCCCGCAACGGGAGGAAGU	3361
rs362300	12902	CUUCCUCCCGUUGCGGGGU	1610	12902	CUUCCUCCCGUUGCGGGGU	1610	12920	ACCCCGCAACGGGAGGAAG	3362
rs362300	12903	UUCCUCCCGUUGCGGGGUG	1611	12903	UUCCUCCCGUUGCGGGGUG	1611	12921	CACCCCGCAACGGGAGGAA	3363
rs362300	12904	UCCUCCCGUUGCGGGGUGG	1612	12904	UCCUCCCGUUGCGGGGUGG	1612	12922	CCACCCCGCAACGGGAGGA	3364
rs362300	12905	CCUCCCGUUGCGGGGUGGA	1613	12905	CCUCCCGUUGCGGGGUGGA	1613	12923	UCCACCCCGCAACGGGAGG	3365
rs362300	12906	CUCCCGUUGCGGGGUGGAG	1614	12906	CUCCCGUUGCGGGGUGGAG	1614	12924	CUCCACCCCGCAACGGGAG	3366
rs362300	12907	UCCCGUUGCGGGGUGGAGU	1615	12907	UCCCGUUGCGGGGUGGAGU	1615	12925	ACUCCACCCCGCAACGGGA	3367
rs362300	12908	CCCGUUGCGGGGUGGAGUG	1616	12908	CCCGUUGCGGGGUGGAGUG	1616	12926	CACUCCACCCCGCAACGGG	3368
rs362300	12909	CCGUUGCGGGGUGGAGUGA	1617	12909	CCGUUGCGGGGUGGAGUGA	1617	12927	UCACUCCACCCCGCAACGG	3369
rs362300	12910	CGUUGCGGGGUGGAGUGAG	1618	12910	CGUUGCGGGGUGGAGUGAG	1618	12928	CUCACUCCACCCCGCAACG	3370
rs362300	12911	GUUGCGGGGUGGAGUGAGG	1619	12911	GUUGCGGGGUGGAGUGAGG	1619	12929	CCUCACUCCACCCCGCAAC	3371
rs362300	12893	CAGGUGGAACUUCCUCCCA	1620	12893	CAGGUGGAACUUCCUCCCA	1620	12911	UGGGAGGAAGUUCCACCUG	3372
rs362300	12894	AGGUGGAACUUCCUCCCAU	1621	12894	AGGUGGAACUUCCUCCCAU	1621	12912	AUGGGAGGAAGUUCCACCU	3373
rs362300	12895	GGUGGAACUUCCUCCCAUU	1622	12895	GGUGGAACUUCCUCCCAUU	1622	12913	AAUGGGAGGAAGUUCCACC	3374
rs362300	12896	GUGGAACUUCCUCCCAUUG	1623	12896	GUGGAACUUCCUCCCAUUG	1623	12914	CAAUGGGAGGAAGUUCCAC	3375
rs362300	12897	UGGAACUUCCUCCCAUUGC	1624	12897	UGGAACUUCCUCCCAUUGC	1624	12915	GCAAUGGGAGGAAGUUCCA	3376
rs362300	12898	GGAACUUCCUCCCAUUGCG	1625	12898	GGAACUUCCUCCCAUUGCG	1625	12916	CGCAAUGGGAGGAAGUUCC	3377
rs362300	12899	GAACUUCCUCCCAUUGCGG	1626	12899	GAACUUCCUCCCAUUGCGG	1626	12917	CCGCAAUGGGAGGAAGUUC	3378
rs362300	12900	AACUUCCUCCCAUUGCGGG	1627	12900	AACUUCCUCCCAUUGCGGG	1627	12918	CCCGCAAUGGGAGGAAGUU	3379
rs362300	12901	ACUUCCUCCCAUUGCGGGG	1628	12901	ACUUCCUCCCAUUGCGGGG	1628	12919	CCCCGCAAUGGGAGGAAGU	3380
rs362300	12902	CUUCCUCCCAUUGCGGGGU	1629	12902	CUUCCUCCCAUUGCGGGGU	1629	12920	ACCCCGCAAUGGGAGGAAG	3381
rs362300	12903	UUCCUCCCAUUGCGGGGUG	1630	12903	UUCCUCCCAUUGCGGGGUG	1630	12921	CACCCCGCAAUGGGAGGAA	3382
rs362300	12904	UCCUCCCAUUGCGGGGUGG	1631	12904	UCCUCCCAUUGCGGGGUGG	1631	12922	CCACCCCGCAAUGGGAGGA	3383
rs362300	12905	CCUCCCAUUGCGGGGUGGA	1632	12905	CCUCCCAUUGCGGGGUGGA	1632	12923	UCCACCCCGCAAUGGGAGG	3384
rs362300	12906	CUCCCAUUGCGGGGUGGAG	1633	12906	CUCCCAUUGCGGGGUGGAG	1633	12924	CUCCACCCCGCAAUGGGAG	3385
rs362300	12907	UCCCAUUGCGGGGUGGAGU	1634	12907	UCCCAUUGCGGGGUGGAGU	1634	12925	ACUCCACCCCGCAAUGGGA	3386

rs362300	12908	CCCAUUGCGGGGUGGAGUG	1635	12908	CCCAUUGCGGGGUGGAGUG	1635	12926	CACUCCACCCCGCAAUGGG	3387
rs362300	12909	CCAUUGCGGGGUGGAGUGA	1636	12909	CCAUUGCGGGGUGGAGUGA	1636	12927	UCACUCCACCCCGCAAUGG	3388
rs362300	12910	CAUUGCGGGGUGGAGUGAG	1637	12910	CAUUGCGGGGUGGAGUGAG	1637	12928	CUCACUCCACCCCGCAAUG	3389
rs362300	12911	AUUGCGGGGUGGAGUGAGG	1638	12911	AUUGCGGGGUGGAGUGAGG	1638	12929	CCUCACUCCACCCCGCAAU	3390
rs2530595	13022	CCCCGCUUCCUCCCCUCUGC	1639	13022	CCCCGCUUCCUCCCCUCUGC	1639	13040	GCAGAGGGAGGAAGCGGGG	3391
rs2530595	13023	CCCGCUUCCUCCCCUCUGCG	1640	13023	CCCGCUUCCUCCCCUCUGCG	1640	13041	CGCAGAGGGAGGAAGCGGG	3392
rs2530595	13024	CCGCUUCCUCCCCUCUGCGG	1641	13024	CCGCUUCCUCCCCUCUGCGG	1641	13042	CCGCAGAGGGAGGAAGCGG	3393
rs2530595	13025	CGCUUCCUCCCCUCUGCGGG	1642	13025	CGCUUCCUCCCCUCUGCGGG	1642	13043	CCCGCAGAGGGAGGAAGCG	3394
rs2530595	13026	GCUUCCUCCCCUCUGCGGGG	1643	13026	GCUUCCUCCCCUCUGCGGGG	1643	13044	CCCCGCAGAGGGAGGAAGC	3395
rs2530595	13027	CUUCCUCCCCUCUGCGGGGA	1644	13027	CUUCCUCCCCUCUGCGGGGA	1644	13045	UCCCCGCAGAGGGAGGAAG	3396
rs2530595	13028	UUCCUCCCCUCUGCGGGGAG	1645	13028	UUCCUCCCCUCUGCGGGGAG	1645	13046	CUCCCCGCAGAGGGAGGAA	3397
rs2530595	13029	UCCUCCCCUCUGCGGGGAGG	1646	13029	UCCUCCCCUCUGCGGGGAGG	1646	13047	CCUCCCCGCAGAGGGAGGA	3398
rs2530595	13030	CCUCCCCUCUGCGGGGAGGA	1647	13030	CCUCCCCUCUGCGGGGAGGA	1647	13048	UCCUCCCCGCAGAGGGAGG	3399
rs2530595	13031	CUCCCUCUGCGGGGAGGAC	1648	13031	CUCCCUCUGCGGGGAGGAC	1648	13049	GUCCUCCCCGCAGAGGGAG	3400
rs2530595	13032	UCCCUCUGCGGGGAGGACC	1649	13032	UCCCUCUGCGGGGAGGACC	1649	13050	GGUCCUCCCCGCAGAGGGA	3401
rs2530595	13033	CCCUCUGCGGGGAGGACCC	1650	13033	CCCUCUGCGGGGAGGACCC	1650	13051	GGGUCCUCCCCGCAGAGGG	3402
rs2530595	13034	CCUCUGCGGGGAGGACCCG	1651	13034	CCUCUGCGGGGAGGACCCG	1651	13052	CGGGUCCUCCCCGCAGAGG	3403
rs2530595	13035	CUCUGCGGGGAGGACCCGG	1652	13035	CUCUGCGGGGAGGACCCGG	1652	13053	CCGGGUCCUCCCCGCAGAG	3404
rs2530595	13036	UCUGCGGGGAGGACCCGGG	1653	13036	UCUGCGGGGAGGACCCGGG	1653	13054	CCCGGGUCCUCCCCGCAGA	3405
rs2530595	13037	CUGCGGGGAGGACCCGGGA	1654	13037	CUGCGGGGAGGACCCGGGA	1654	13055	UCCCGGGUCCUCCCCGCAG	3406
rs2530595	13038	UGCGGGGAGGACCCGGGAC	1655	13038	UGCGGGGAGGACCCGGGAC	1655	13056	GUCCCGGGUCCUCCCCGCA	3407
rs2530595	13039	GCGGGGAGGACCCGGGACC	1656	13039	GCGGGGAGGACCCGGGACC	1656	13057	GGUCCCGGGUCCUCCCCGC	3408
rs2530595	13040	CGGGGAGGACCCGGGACCA	1657	13040	CGGGGAGGACCCGGGACCA	1657	13058	UGGUCCCGGGUCCUCCCCG	3409
rs2530595	13022	CCCCGCUUCCUCCCCUCUGU	1658	13022	CCCCGCUUCCUCCCCUCUGU	1658	13040	ACAGAGGGAGGAAGCGGGG	3410
rs2530595	13023	CCCGCUUCCUCCCCUCUGUG	1659	13023	CCCGCUUCCUCCCCUCUGUG	1659	13041	CACAGAGGGAGGAAGCGGG	3411
rs2530595	13024	CCGCUUCCUCCCCUCUGUGG	1660	13024	CCGCUUCCUCCCCUCUGUGG	1660	13042	CCACAGAGGGAGGAAGCGG	3412
rs2530595	13025	CGCUUCCUCCCCUCUGUGGG	1661	13025	CGCUUCCUCCCCUCUGUGGG	1661	13043	CCCACAGAGGGAGGAAGCG	3413
rs2530595	13026	GCUUCCUCCCCUCUGUGGGG	1662	13026	GCUUCCUCCCCUCUGUGGGG	1662	13044	CCCCACAGAGGGAGGAAGC	3414
rs2530595	13027	CUUCCUCCCCUCUGUGGGGA	1663	13027	CUUCCUCCCCUCUGUGGGGA	1663	13045	UCCCCACAGAGGGAGGAAG	3415
rs2530595	13028	UUCCUCCCCUCUGUGGGGAG	1664	13028	UUCCUCCCCUCUGUGGGGAG	1664	13046	CUCCCCACAGAGGGAGGAA	3416
rs2530595	13029	UCCUCCCCUCUGUGGGGAGG	1665	13029	UCCUCCCCUCUGUGGGGAGG	1665	13047	CCUCCCCACAGAGGGAGGA	3417
rs2530595	13030	CCUCCCCUCUGUGGGGAGGA	1666	13030	CCUCCCCUCUGUGGGGAGGA	1666	13048	UCCUCCCCACAGAGGGAGG	3418
rs2530595	13031	CUCCCCUCUGUGGGGAGGAC	1667	13031	CUCCCCUCUGUGGGGAGGAC	1667	13049	GUCCUCCCCACAGAGGGAG	3419
rs2530595	13032	UCCCCUCUGUGGGGAGGACC	1668	13032	UCCCCUCUGUGGGGAGGACC	1668	13050	GGUCCUCCCCACAGAGGGA	3420
rs2530595	13033	CCCCUCUGUGGGGAGGACCC	1669	13033	CCCCUCUGUGGGGAGGACCC	1669	13051	GGGUCCUCCCCACAGAGGG	3421
rs2530595	13034	CCUCUGUGGGGAGGACCCG	1670	13034	CCUCUGUGGGGAGGACCCG	1670	13052	CGGGUCCUCCCCACAGAGG	3422
rs2530595	13035	CUCUGUGGGGAGGACCCGG	1671	13035	CUCUGUGGGGAGGACCCGG	1671	13053	CCGGGUCCUCCCCACAGAG	3423
rs2530595	13036	UCUGUGGGGAGGACCCGGG	1672	13036	UCUGUGGGGAGGACCCGGG	1672	13054	CCCGGGUCCUCCCCACAGA	3424
rs2530595	13037	CUGUGGGGAGGACCCGGGA	1673	13037	CUGUGGGGAGGACCCGGGA	1673	13055	UCCCGGGUCCUCCCCACAG	3425

rs2530595	13038	UGUGGGGAGGACCCGGGAC	1674	13038	UGUGGGGAGGACCCGGGAC	1674	13056	GUCCCGGGUCCUCCCCACA	3426
rs2530595	13039	GUGGGGAGGACCCGGGACC	1675	13039	GUGGGGAGGACCCGGGACC	1675	13057	GGUCCCGGGUCCUCCCCAC	3427
rs2530595	13040	UGGGGAGGACCCGGGACCA	1676	13040	UGGGGAGGACCCGGGACCA	1676	13058	UGGUCCCGGGUCCUCCCCA	3428
rs1803770	13464	CUGCUUUGCACCGUGGUCA	1677	13464	CUGCUUUGCACCGUGGUCA	1677	13482	UGACCACGGUGCAAAGCAG	3429
rs1803770	13465	UGCUUUGCACCGUGGUCAG	1678	13465	UGCUUUGCACCGUGGUCAG	1678	13483	CUGACCACGGUGCAAAGCA	3430
rs1803770	13466	GCUUUGCACCGUGGUCAGA	1679	13466	GCUUUGCACCGUGGUCAGA	1679	13484	UCUGACCACGGUGCAAAGC	3431
rs1803770	13467	CUUUGCACCGUGGUCAGAG	1680	13467	CUUUGCACCGUGGUCAGAG	1680	13485	CUCUGACCACGGUGCAAAG	3432
rs1803770	13468	UUUGCACCGUGGUCAGAGG	1681	13468	UUUGCACCGUGGUCAGAGG	1681	13486	CCUCUGACCACGGUGCAAA	3433
rs1803770	13469	UUGCACCGUGGUCAGAGGG	1682	13469	UUGCACCGUGGUCAGAGGG	1682	13487	CCCUCUGACCACGGUGCAA	3434
rs1803770	13470	UGCACCGUGGUCAGAGGGA	1683	13470	UGCACCGUGGUCAGAGGGA	1683	13488	UCCCUCUGACCACGGUGCA	3435
rs1803770	13471	GCACCGUGGUCAGAGGGAC	1684	13471	GCACCGUGGUCAGAGGGAC	1684	13489	GUCCCUCUGACCACGGUGC	3436
rs1803770	13472	CACCGUGGUCAGAGGGACU	1685	13472	CACCGUGGUCAGAGGGACU	1685	13490	AGUCCCUCUGACCACGGUG	3437
rs1803770	13473	ACCGUGGUCAGAGGGACUG	1686	13473	ACCGUGGUCAGAGGGACUG	1686	13491	CAGUCCCUCUGACCACGGU	3438
rs1803770	13474	CCGUGGUCAGAGGGACUGU	1687	13474	CCGUGGUCAGAGGGACUGU	1687	13492	ACAGUCCCUCUGACCACGG	3439
rs1803770	13475	CGUGGUCAGAGGGACUGUC	1688	13475	CGUGGUCAGAGGGACUGUC	1688	13493	GACAGUCCCUCUGACCACG	3440
rs1803770	13476	GUGGUCAGAGGGACUGUCA	1689	13476	GUGGUCAGAGGGACUGUCA	1689	13494	UGACAGUCCCUCUGACCAC	3441
rs1803770	13477	UGGUCAGAGGGACUGUCAG	1690	13477	UGGUCAGAGGGACUGUCAG	1690	13495	CUGACAGUCCCUCUGACCA	3442
rs1803770	13478	GGUCAGAGGGACUGUCAGC	1691	13478	GGUCAGAGGGACUGUCAGC	1691	13496	GCUGACAGUCCCUCUGACC	3443
rs1803770	13479	GUCAGAGGGACUGUCAGCU	1692	13479	GUCAGAGGGACUGUCAGCU	1692	13497	AGCUGACAGUCCCUCUGAC	3444
rs1803770	13480	UCAGAGGGACUGUCAGCUG	1693	13480	UCAGAGGGACUGUCAGCUG	1693	13498	CAGCUGACAGUCCCUCUGA	3445
rs1803770	13481	CAGAGGGACUGUCAGCUGA	1694	13481	CAGAGGGACUGUCAGCUGA	1694	13499	UCAGCUGACAGUCCCUCUG	3446
rs1803770	13482	AGAGGGACUGUCAGCUGAG	1695	13482	AGAGGGACUGUCAGCUGAG	1695	13500	CUCAGCUGACAGUCCCUCU	3447
rs1803770	13464	CUGCUUUGCACCGUGGUCG	1696	13464	CUGCUUUGCACCGUGGUCG	1696	13482	CGACCACGGUGCAAAGCAG	3448
rs1803770	13465	UGCUUUGCACCGUGGUCGG	1697	13465	UGCUUUGCACCGUGGUCGG	1697	13483	CCGACCACGGUGCAAAGCA	3449
rs1803770	13466	GCUUUGCACCGUGGUCGGA	1698	13466	GCUUUGCACCGUGGUCGGA	1698	13484	UCCGACCACGGUGCAAAGC	3450
rs1803770	13467	CUUUGCACCGUGGUCGGAG	1699	13467	CUUUGCACCGUGGUCGGAG	1699	13485	CUCCGACCACGGUGCAAAG	3451
rs1803770	13468	UUUGCACCGUGGUCGGAGG	1700	13468	UUUGCACCGUGGUCGGAGG	1700	13486	CCUCCGACCACGGUGCAAA	3452
rs1803770	13469	UUGCACCGUGGUCGGAGGG	1701	13469	UUGCACCGUGGUCGGAGGG	1701	13487	CCCUCCGACCACGGUGCAA	3453
rs1803770	13470	UGCACCGUGGUCGGAGGGA	1702	13470	UGCACCGUGGUCGGAGGGA	1702	13488	UCCCUCCGACCACGGUGCA	3454
rs1803770	13471	GCACCGUGGUCGGAGGGAC	1703	13471	GCACCGUGGUCGGAGGGAC	1703	13489	GUCCCUCCGACCACGGUGC	3455
rs1803770	13472	CACCGUGGUCGGAGGGACU	1704	13472	CACCGUGGUCGGAGGGACU	1704	13490	AGUCCCUCCGACCACGGUG	3456
rs1803770	13473	ACCGUGGUCGGAGGGACUG	1705	13473	ACCGUGGUCGGAGGGACUG	1705	13491	CAGUCCCUCCGACCACGGU	3457
rs1803770	13474	CCGUGGUCGGAGGGACUGU	1706	13474	CCGUGGUCGGAGGGACUGU	1706	13492	ACAGUCCCUCCGACCACGG	3458
rs1803770	13475	CGUGGUCGGAGGGACUGUC	1707	13475	CGUGGUCGGAGGGACUGUC	1707	13493	GACAGUCCCUCCGACCACG	3459
rs1803770	13476	GUGGUCGGAGGGACUGUCA	1708	13476	GUGGUCGGAGGGACUGUCA	1708	13494	UGACAGUCCCUCCGACCAC	3460
rs1803770	13477	UGGUCGGAGGGACUGUCAG	1709	13477	UGGUCGGAGGGACUGUCAG	1709	13495	CUGACAGUCCCUCCGACCA	3461
rs1803770	13478	GGUCGGAGGGACUGUCAGC	1710	13478	GGUCGGAGGGACUGUCAGC	1710	13496	GCUGACAGUCCCUCCGACC	3462
rs1803770	13479	GUCGGAGGGACUGUCAGCU	1711	13479	GUCGGAGGGACUGUCAGCU	1711	13497	AGCUGACAGUCCCUCCGAC	3463
rs1803770	13480	UCGGAGGGACUGUCAGCUG	1712	13480	UCGGAGGGACUGUCAGCUG	1712	13498	CAGCUGACAGUCCCUCCGA	3464

rs1803770	13481	CGGAGGGACUGUCAGCUGA	1713	13481	CGGAGGGACUGUCAGCUGA	1713	13499	UCAGCUGACAGUCCCUCCG	3465
rs1803770	13482	GGAGGGACUGUCAGCUGAG	1714	13482	GGAGGGACUGUCAGCUGAG	1714	13500	CUCAGCUGACAGUCCCUCC	3466
rs1803771	13545	GGAGCCCCACCCAGACCUG	1715	13545	GGAGCCCCACCCAGACCUG	1715	13563	CAGGUCUGGGUGGGGCUCC	3467
rs1803771	13546	GAGCCCCACCCAGACCUGA	1716	13546	GAGCCCCACCCAGACCUGA	1716	13564	UCAGGUCUGGGUGGGGCUC	3468
rs1803771	13547	AGCCCCACCCAGACCUGAA	1717	13547	AGCCCCACCCAGACCUGAA	1717	13565	UUCAGGUCUGGGUGGGGCU	3469
rs1803771	13548	GCCCCACCCAGACCUGAAU	1718	13548	GCCCCACCCAGACCUGAAU	1718	13566	AUUCAGGUCUGGGUGGGGC	3470
rs1803771	13549	CCCCACCCAGACCUGAAUG	1719	13549	CCCCACCCAGACCUGAAUG	1719	13567	CAUUCAGGUCUGGGUGGGG	3471
rs1803771	13550	CCCACCCAGACCUGAAUGC	1720	13550	CCCACCCAGACCUGAAUGC	1720	13568	GCAUUCAGGUCUGGGUGGG	3472
rs1803771	13551	CCACCCAGACCUGAAUGCU	1721	13551	CCACCCAGACCUGAAUGCU	1721	13569	AGCAUUCAGGUCUGGGUGG	3473
rs1803771	13552	CACCCAGACCUGAAUGCUU	1722	13552	CACCCAGACCUGAAUGCUU	1722	13570	AAGCAUUCAGGUCUGGGUG	3474
rs1803771	13553	ACCCAGACCUGAAUGCUUC	1723	13553	ACCCAGACCUGAAUGCUUC	1723	13571	GAAGCAUUCAGGUCUGGGU	3475
rs1803771	13554	CCCAGACCUGAAUGCUUCU	1724	13554	CCCAGACCUGAAUGCUUCU	1724	13572	AGAAGCAUUCAGGUCUGGG	3476
rs1803771	13555	CCAGACCUGAAUGCUUCUG	1725	13555	CCAGACCUGAAUGCUUCUG	1725	13573	CAGAAGCAUUCAGGUCUGG	3477
rs1803771	13556	CAGACCUGAAUGCUUCUGA	1726	13556	CAGACCUGAAUGCUUCUGA	1726	13574	UCAGAAGCAUUCAGGUCUG	3478
rs1803771	13557	AGACCUGAAUGCUUCUGAG	1727	13557	AGACCUGAAUGCUUCUGAG	1727	13575	CUCAGAAGCAUUCAGGUCU	3479
rs1803771	13558	GACCUGAAUGCUUCUGAGA	1728	13558	GACCUGAAUGCUUCUGAGA	1728	13576	UCUCAGAAGCAUUCAGGUC	3480
rs1803771	13559	ACCUGAAUGCUUCUGAGAG	1729	13559	ACCUGAAUGCUUCUGAGAG	1729	13577	CUCUCAGAAGCAUUCAGGU	3481
rs1803771	13560	CCUGAAUGCUUCUGAGAGC	1730	13560	CCUGAAUGCUUCUGAGAGC	1730	13578	GCUCUCAGAAGCAUUCAGG	3482
rs1803771	13561	CUGAAUGCUUCUGAGAGCA	1731	13561	CUGAAUGCUUCUGAGAGCA	1731	13579	UGCUCUCAGAAGCAUUCAG	3483
rs1803771	13562	UGAAUGCUUCUGAGAGCAA	1732	13562	UGAAUGCUUCUGAGAGCAA	1732	13580	UUGCUCUCAGAAGCAUUCA	3484
rs1803771	13563	GAAUGCUUCUGAGAGCAAA	1733	13563	GAAUGCUUCUGAGAGCAAA	1733	13581	UUUGCUCUCAGAAGCAUUC	3485
rs1803771	13545	GGAGCCCCACCCAGACCUA	1734	13545	GGAGCCCCACCCAGACCUA	1734	13563	UAGGUCUGGGUGGGGCUCC	3486
rs1803771	13546	GAGCCCCACCCAGACCUAA	1735	13546	GAGCCCCACCCAGACCUAA	1735	13564	UUAGGUCUGGGUGGGGCUC	3487
rs1803771	13547	AGCCCCACCCAGACCUAAA	1736	13547	AGCCCCACCCAGACCUAAA	1736	13565	UUUAGGUCUGGGUGGGGCU	3488
rs1803771	13548	GCCCCACCCAGACCUAAAU	1737	13548	GCCCCACCCAGACCUAAAU	1737	13566	AUUUAGGUCUGGGUGGGGC	3489
rs1803771	13549	CCCCACCCAGACCUAAAUG	1738	13549	CCCCACCCAGACCUAAAUG	1738	13567	CAUUUAGGUCUGGGUGGGG	3490
rs1803771	13550	CCCACCCAGACCUAAAUGC	1739	13550	CCCACCCAGACCUAAAUGC	1739	13568	GCAUUUAGGUCUGGGUGGG	3491
rs1803771	13551	CCACCCAGACCUAAAUGCU	1740	13551	CCACCCAGACCUAAAUGCU	1740	13569	AGCAUUUAGGUCUGGGUGG	3492
rs1803771	13552	CACCCAGACCUAAAUGCUU	1741	13552	CACCCAGACCUAAAUGCUU	1741	13570	AAGCAUUUAGGUCUGGGUG	3493
rs1803771	13553	ACCCAGACCUAAAUGCUUC	1742	13553	ACCCAGACCUAAAUGCUUC	1742	13571	GAAGCAUUUAGGUCUGGGU	3494
rs1803771	13554	CCCAGACCUAAAUGCUUCU	1743	13554	CCCAGACCUAAAUGCUUCU	1743	13572	AGAAGCAUUUAGGUCUGGG	3495
rs1803771	13555	CCAGACCUAAAUGCUUCUG	1744	13555	CCAGACCUAAAUGCUUCUG	1744	13573	CAGAAGCAUUUAGGUCUGG	3496
rs1803771	13556	CAGACCUAAAUGCUUCUGA	1745	13556	CAGACCUAAAUGCUUCUGA	1745	13574	UCAGAAGCAUUUAGGUCUG	3497
rs1803771	13557	AGACCUAAAUGCUUCUGAG	1746	13557	AGACCUAAAUGCUUCUGAG	1746	13575	CUCAGAAGCAUUUAGGUCU	3498
rs1803771	13558	GACCUAAAUGCUUCUGAGA	1747	13558	GACCUAAAUGCUUCUGAGA	1747	13576	UCUCAGAAGCAUUUAGGUC	3499
rs1803771	13559	ACCUAAAUGCUUCUGAGAG	1748	13559	ACCUAAAUGCUUCUGAGAG	1748	13577	CUCUCAGAAGCAUUUAGGU	3500
rs1803771	13560	CCUAAAUGCUUCUGAGAGC	1749	13560	CCUAAAUGCUUCUGAGAGC	1749	13578	GCUCUCAGAAGCAUUUAGG	3501
rs1803771	13561	CUAAAUGCUUCUGAGAGCA	1750	13561	CUAAAUGCUUCUGAGAGCA	1750	13579	UGCUCUCAGAAGCAUUUAG	3502
rs1803771	13562	UAAAUGCUUCUGAGAGCAA	1751	13562	UAAAUGCUUCUGAGAGCAA	1751	13580	UUGCUCUCAGAAGCAUUUA	3503

rs1803771	13563	AAAUGCUUCUGAGAGCAAA	1752	13563	AAAUGCUUCUGAGAGCAAA	1752	13581	UUUGCUCUCAGAAGCAUUU	3504

The 3'-ends of the Upper sequence and the Lower sequence of the siNA construct can include an overhang sequence, for example about 1, 2, 3, or 4 nucleotides in length, preferably 2 nucleotides in length, wherein the overhanging sequence of the lower sequence is optionally complementary to a portion of the target sequence. The overhang can comprise the general structure B, BNN, NN, BNsN, or NsN, where B stands for any terminal cap moiety, N stands for any nucleotide (e.g., thymidine) and s stands for phosphorothioate or other internucleotide linkage as described herein (e.g. internucleotide linkage having Formula I). The upper sequence is also referred to as the sense strand, whereas the lower sequence is also referred to as the antisense strand. The upper and lower sequences in the Table can further comprise a chemical modification having Formulae I-VII or any combination thereof (see for example chemical modifications as shown in Table V herein).

Table III: HD synthetic siNA and Target Sequences

Target Pos	Target	SeqID	Sirna #	Aliases	Sequence	SeqID
586	CAAAGAAAGAACUUUCAGCUACC	3505	31993	HD:586U21 sense	AAGAAAGAACUUUCAGCUATT	3512
586	CAAAGAAAGAACUUUCAGCUACC	3505	31994	HD:604L21 (586C) antisense	UAGCUGAAAGUUCUUUCUUTT	3513
586	CAAAGAAAGAACUUUCAGCUACC	3505	31995	HD:586U21 stab04 sense	B AAGAAAGAAcuuucAGcuATT B	3514
586	CAAAGAAAGAACUUUCAGCUACC	3505	31996	HD:604L21 (586C) stab05 antisense	uAGcuGAAAGuucuuucuuTsT	3515
586	CAAAGAAAGAACUUUCAGCUACC	3505	31997	HD:586U21 stab07 sense	B *AAGAAAGAA*cuuuc*AG*cu*A*TT B	3516
586	CAAAGAAAGAACUUUCAGCUACC	3505	31998	HD:604L21 (586C) stab08 antisense	uAGcuGAAAGuucuuucuuTsT	3517
586	CAAAGAAAGAACUUUCAGCUACC	3505	31999	HD:586U21 inv sense	AUCGACUUUCAAGAAAGAATT	3518
586	CAAAGAAAGAACUUUCAGCUACC	3505	32000	HD:604L21 (586C) inv antisense	UUCUUUCUUGAAAGUCGAUTT	3519
586	CAAAGAAAGAACUUUCAGCUACC	3505	32001	HD:586U21 inv stab04 sense	B AucGAcuuucAAGAAAGAATT B	3520
586	CAAAGAAAGAACUUUCAGCUACC	3505	32002	HD:604L21 (586C) inv stab05 antisense	uucuuucuuGAAAGucGAuTsT	3521
586	CAAAGAAAGAACUUUCAGCUACC	3505	32003	HD:586U21 inv stab07 sense	B *Auc*G*A*cuuuc*AAGAAAGAA*TT B	3522
586	CAAAGAAAGAACUUUCAGCUACC	3505	32004	HD:604L21 (586C) inv stab08 antisense	uucuuucuuGAAAGucGAuTsT	3523
316	CCAUGGCGACCCUGGAAAAGCUG	3506	33065	HD:316U21 siRNA stab04 sense	B AuGGcGAcccuGGAAAAGcTT B	3524
591	AAAGAACUUUCAGCUACCAAGAA	3507	33066	HD:591U21 siRNA stab04 sense	B AGAAcuuucAGcuAccAAGTT B	3525
671	AAAUUCUCCAGAAUUUCAGAAAC	3508	33067	HD:671U21 siRNA stab04 sense	B AuucuccAGAAuuucAGAATT B	3526
769	AAUGCCUCAACAAAGUUAUCAAA	3509	33068	HD:769U21 siRNA stab04 sense	B uGccucAAcAAAGuuAucATT B	3527
1	GAGGAAGAGGAGGAGGCCGAC	3510	33069	HD-Ex58:3U21 siRNA stab04 sense	B GGAAGAGGAGGAGGccGAcTT B	3528
2	AAGAGGAGGAGGCCGACGCCC	3511	33070	HD-Ex58:7U21 siRNA stab04 sense	B GAGGAGGAGGccGAcGcccTT B	3529
316	CCAUGGCGACCCUGGAAAAGCUG	3506	33071	HD:334L21 siRNA (316C) stab05 antisense	GcuuuuccAGGGucGccAuTsT	3530
591	AAAGAACUUUCAGCUACCAAGAA	3507	33072	HD:609L21 siRNA (591C) stab05 antisense	cuuGGuAGcuGAAAGuucuTsT	3531
671	AAAUUCUCCAGAAUUUCAGAAAC	3508	33073	HD:689L21 siRNA (671C) stab05 antisense	uucuGAAAuucuGGAGAAuTsT	3532
769	AAUGCCUCAACAAAGUUAUCAAA	3509	33074	HD:787L21 siRNA (769C) stab05 antisense	uGAuAAcuuuGuuGAGGcATsT	3533
1	GAGGAAGAGGAGGAGGCCGAC	3510	33075	HD-Ex58:21L21 siRNA (Ex58-3C) stab05 antisense	GucGGccuccuccucuuccTsT	3534
2	AAGAGGAGGAGGCCGACGCCC	3511	33076	HD-Ex58:25L21 siRNA (Ex58-7C) stab05 antisense	GGGcGucGGccuccuccucTsT	3535
316	CCAUGGCGACCCUGGAAAAGCUG	3506	33077	HD:316U21 siRNA stab07 sense	B *AuGGcGA*cccu*GGAAAAG*cTT B	3536
591	AAAGAACUUUCAGCUACCAAGAA	3507	33078	HD:591U21 siRNA stab07 sense	B *AGAA*cuuuc*AG*cu*Acc**AAG*TT B	3537
671	AAAUUCUCCAGAAUUUCAGAAAC	3508	33079	HD:671U21 siRNA stab07 sense	B *Auucucc**AGAA*uuuc*AGAA*TT B	3538
769	AAUGCCUCAACAAAGUUAUCAAA	3509	33080	HD:769U21 siRNA stab07 sense	B u*GccucAAcAAAG*uu*AucA*TT B	3539

1	GAGGAAGAGGAGGAGGCCGAC	3510	33081	HD-Ex58:3U21 siRNA stab07 sense	B *GGAAGAGGAGGAGG*ccGAcTT B	3540
2	AAGAGGAGGAGGCCGACGCCC	3511	33082	HD-Ex58:7U21 siRNA stab07 sense	B *GAGGAGGAGG*ccGAcGcccTT B	3541
316	CCAUGGCGACCCUGGAAAAGCUG	3506	33083	HD:334L21 siRNA (316C) stab08 antisense	GcuuuuccAGGGucGccAuTsT	3542
591	AAAGAACUUUCAGCUACCAAGAA	3507	33084	HD:609L21 siRNA (591C) stab08 antisense	cuuGGuAGcuGAAAGuucuTsT	3543
671	AAAUUCUCCAGAAUUUCAGAAAC	3508	33085	HD:689L21 siRNA (671C) stab08 antisense	uucuGAAAuucuGGAGAAuTsT	3544
769	AAUGCCUCAACAAAGUUAUCAAA	3509	33086	HD:787L21 siRNA (769C) stab08 antisense	uGAuAAcuuuGuuGAGGcATsT	3545
1	GAGGAAGAGGAGGAGGCCGAC	3510	33087	HD-Ex58:21L21 siRNA (Ex58-3C) stab08 antisense	GucGGccuccuccucuuccTsT	3546
2	AAGAGGAGGAGGCCGACGCCC	3511	33088	HD-Ex58:25L21 siRNA (Ex58-7C) stab08 antisense	GGGcGucGGccuccuccucTsT	3547
316	CCAUGGCGACCCUGGAAAAGCUG	3506	33089	HD:316U21 siRNA stab09 sense	B AUGGCGACCCUGGAAAAGCTT B	3548
591	AAAGAACUUUCAGCUACCAAGAA	3507	33090	HD:591U21 siRNA stab09 sense	B AGAACUUUCAGCUACCAAGTT B	3549
671	AAAUUCUCCAGAAUUUCAGAAAC	3508	33091	HD:671U21 siRNA stab09 sense	B AUUCUCCAGAAUUUCAGAATT B	3550
769	AAUGCCUCAACAAAGUUAUCAAA	3509	33092	HD:769U21 siRNA stab09 sense	B UGCCUCAACAAAGUUAUCATT B	3551
1	GAGGAAGAGGAGGAGGCCGAC	3510	33093	HD-Ex58:3U21 siRNA stab09 sense	B GGAAGAGGAGGAGGCCGACTT B	3552
2	AAGAGGAGGAGGCCGACGCCC	3511	33094	HD-Ex58:7U21 siRNA stab09 sense	B GAGGAGGAGGCCGACGCCCTT B	3553
316	CCAUGGCGACCCUGGAAAAGCUG	3506	33095	HD:334L21 siRNA (316C) stab10 antisense	GCUUUUCCAGGGUCGCCAUTsT	3554
591	AAAGAACUUUCAGCUACCAAGAA	3507	33096	HD:609L21 siRNA (591C) stab10 antisense	CUUGGUAGCUGAAAGUUCUTsT	3555
671	AAAUUCUCCAGAAUUUCAGAAAC	3508	33097	HD:689L21 siRNA (671C) stab10 antisense	UUCUGAAAUUCUGGAGAAUTsT	3556
769	AAUGCCUCAACAAAGUUAUCAAA	3509	33098	HD:787L21 siRNA (769C) stab10 antisense	UGAUAACUUUGUUGAGGCATsT	3557
1	GAGGAAGAGGAGGAGGCCGAC	3510	33099	HD-Ex58:21L21 siRNA (Ex58-3C) stab10 antisense	GUCGGCCUCCUCCUCUUCCTsT	3558
2	AAGAGGAGGAGGCCGACGCCC	3511	33100	HD-Ex58:25L21 siRNA (Ex58-7C) stab10 antisense	GGGCGUCGGCCUCCUCCUCTsT	3559

Uppercase = ribonucleotide	G = 2'-O-methyl Guanosine	R= 5-bromo-deoxy-uridine
u,c = 2'-deoxy-2'-fluoro U,C	X= nitroindole universal base	Z = sbL: symmetrical bifunctional linker
T = thymidine	Z= nitropyrole universal base	H = chol2: capped Cholesterol TEG
B = inverted deoxy abasic	Y= 3',3'-inverted thymidine	A = 2'-O-methyl Adenosine
s = phosphorothioate linkage	M= glyceryl	Q= L-uridine
A = deoxy Adenosine	N= 3'-O-methyl uridine	
G = deoxy Guanosine	P= L-thymidine	

Table IV

Non-limiting examples of Stabilization Chemistries for chemically modified siNA constructs

Chemistry	pyrimidine	Purine	cap	p=S	Strand
"Stab 00"	Ribo	Ribo	TT at 3'-ends		S/AS
"Stab 1"	Ribo	Ribo	-	5 at 5'-end 1 at 3'-end	S/AS
"Stab 2"	Ribo	Ribo	-	All linkages	Usually AS
"Stab 3"	2'-fluoro	Ribo	-	4 at 5'-end 4 at 3'-end	Usually S
"Stab 4"	2'-fluoro	Ribo	5' and 3'-ends	-	Usually S
"Stab 5"	2'-fluoro	Ribo	-	1 at 3'-end	Usually AS
"Stab 6"	2'-O-Methyl	Ribo	5' and 3'-ends	-	Usually S
"Stab 7"	2'-fluoro	2'-deoxy	5' and 3'-ends	-	Usually S
"Stab 8"	2'-fluoro	2'-O-Methyl	-	1 at 3'-end	Usually AS
"Stab 9"	Ribo	Ribo	5' and 3'-ends	-	Usually S
"Stab 10"	Ribo	Ribo	-	1 at 3'-end	Usually AS
"Stab 11"	2'-fluoro	2'-deoxy	-	1 at 3'-end	Usually AS
"Stab 12"	2'-fluoro	LNA	5' and 3'-ends		Usually S
"Stab 13"	2'-fluoro	LNA		1 at 3'-end	Usually AS
"Stab 14"	2'-fluoro	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 15"	2'-deoxy	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 16	Ribo	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 17"	2'-O-Methyl	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 18"	2'-fluoro	2'-O-Methyl	5' and 3'-ends	1 at 3'-end	Usually S
"Stab 19"	2'-fluoro	2'-O-Methyl	3'-end		Usually AS
"Stab 20"	2'-fluoro	2'-deoxy	3'-end		Usually AS
"Stab 21"	2'-fluoro	Ribo	3'-end		Usually AS
"Stab 22"	Ribo	Ribo	3'-end -		Usually AS

CAP = any terminal cap, see for example **Figure 10**.
All Stab 1-22 chemistries can comprise 3'-terminal thymidine (TT) residues
All Stab 1-22 chemistries typically comprise about 21 nucleotides, but can vary as described herein.
S = sense strand AS = antisense strand

Table V

A. 2.5 µmol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	6.5	163 µL	45 sec	2.5 min	7.5 min
S-Ethyl Tetrazole	23.8	238 µL	45 sec	2.5 min	7.5 min
Acetic Anhydride	100	233 µL	5 sec	5 sec	5 sec
N-Methyl Imidazole	186	233 µL	5 sec	5 sec	5 sec
TCA	176	2.3 mL	21 sec	21 sec	21 sec
Iodine	11.2	1.7 mL	45 sec	45 sec	45 sec
Beaucage	12.9	645 µL	100 sec	300 sec	300 sec
Acetonitrile	NA	6.67 mL	NA	NA	NA

B. 0.2 µmol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	15	31 µL	45 sec	233 sec	465 sec
S-Ethyl Tetrazole	38.7	31 µL	45 sec	233 min	465 sec
Acetic Anhydride	655	124 µL	5 sec	5 sec	5 sec
N-Methyl Imidazole	1245	124 µL	5 sec	5 sec	5 sec
TCA	700	732 µL	10 sec	10 sec	10 sec
Iodine	20.6	244 µL	15 sec	15 sec	15 sec
Beaucage	7.7	232 µL	100 sec	300 sec	300 sec
Acetonitrile	NA	2.64 mL	NA	NA	NA

C. 0.2 µmol Synthesis Cycle 96 well Instrument

Reagent	Equivalents:DNA/ 2'-O-methyl/Ribo	Amount: DNA/2'-O-methyl/Ribo	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time* Ribo
Phosphoramidites	22/33/66	40/60/120 µL	60 sec	180 sec	360sec
S-Ethyl Tetrazole	70/105/210	40/60/120 µL	60 sec	180 min	360 sec
Acetic Anhydride	265/265/265	50/50/50 µL	10 sec	10 sec	10 sec
N-Methyl Imidazole	502/502/502	50/50/50 µL	10 sec	10 sec	10 sec
TCA	238/475/475	250/500/500 µL	15 sec	15 sec	15 sec
Iodine	6.8/6.8/6.8	80/80/80 µL	30 sec	30 sec	30 sec
Beaucage	34/51/51	80/120/120	100 sec	200 sec	200 sec
Acetonitrile	NA	1150/1150/1150 µL	NA	NA	NA

- Wait time does not include contact time during delivery.
- Tandem synthesis utilizes double coupling of linker molecule